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(21) International Application Number: PCT/US96/20511 (22) International Filing Date: 16 December 1996 (16.12.96) (30) Priority Data: 08/580,553 29 December 1995 (29.12.95) US (71) Applicant: ALLERGAN [US/US]; 8301 Mars Drive, Waco, TX 76712 (US). (72) Inventors: TENG, Min; 2 Dove Street, Aliso Viejo, CA 92656 (US). DUONG, Tien, T.; Apartment 15C, 13 Bearpaw, Irvine, CA 92714 (US). CHANDRARATNA, Roshantha, A.; 25841 Empresa, Mission Viejo, CA 92691 (US). (74) Agents: BARAN, Robert, J. et al.; Allergan, Inc., 2525 Dupont Drive, T-2,2-E, P.O. Box 19534, Irvine, CA 92623-9534 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: METHODS OF TREATMENT WITH COMPOUNDS HAVING RAR α RECEPTOR SPECIFIC OR SELECTIVE ACTIVITY (57) Abstract <p>Retinoid compounds which act specifically or selectively on RARα receptor subtypes in preference over RARβ and RARγ receptor subtypes, possess desirable pharmaceutical properties associated with retinoids, and are particularly suitable for treatment of tumors, such as acute monocytic leukemia, cervical carcinoma, myeloma, ovarian carcinomas and head and neck carcinomas, without having one or more undesirable side effects of retinoids, such as inducement of weight loss, mucocutaneous toxicity, skin irritation and teratogenicity.</p>		

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1 METHODS OF TREATMENT WITH COMPOUNDS HAVING RAR_α
2 RECEPTOR SPECIFIC OR SELECTIVE ACTIVITY

3 BACKGROUND OF THE INVENTION

4 1. Field of the Invention

5 The present invention relates to the use of
6 compounds which have specific or selective agonist
7 like activity on RAR_α retinoid receptors for
8 treatment of diseases and conditions which respond
9 to treatment by such retinoids. More particularly
10 the present invention is directed to the use of RAR_α
11 receptor specific or selective agents for the
12 treatment of tumors.

13 2. Background Art

14 Compounds which have retinoid-like activity are
15 well known in the art, and are described in numerous
16 United States and other patents and in scientific
17 publications. It is generally known and accepted in
18 the art that retinoid-like activity is useful for
19 treating animals of the mammalian species, including
20 humans, for curing or alleviating the symptoms and
21 conditions of numerous diseases and conditions. In
22 other words, it is generally accepted in the art
23 that pharmaceutical compositions having a
24 retinoid-like compound or compounds as the active
25 ingredient are useful as regulators of cell
26 proliferation and differentiation, and particularly
27 as agents for treating skin-related diseases,
28 including, actinic keratoses, arsenic keratoses,
29 inflammatory and non-inflammatory acne, psoriasis,
30 ichthyoses and other keratinization and
31 hyperproliferative disorders of the skin, eczema,
32 atopic dermatitis, Darriers disease, lichen planus,
33 prevention and reversal of glucocorticoid damage
34 (steroid atrophy), as a topical anti-microbial, as
35 skin anti-pigmentation agents and to treat and

1 reverse the effects of age and photo damage to the
2 skin. Retinoid compounds are also useful for the
3 prevention and treatment of cancerous and
4 precancerous conditions, including, premalignant and
5 malignant hyperproliferative diseases such as
6 cancers of the breast, skin, prostate, cervix,
7 uterus, colon, bladder, esophagus, stomach, lung,
8 larynx, oral cavity, blood and lymphatic system,
9 metaplasias, dysplasias, neoplasias, leukoplakias
10 and papillomas of the mucous membranes and in the
11 treatment of Kaposi's sarcoma. In addition,
12 retinoid compounds can be used as agents to treat
13 diseases of the eye, including, without limitation,
14 proliferative vitreoretinopathy (PVR), retinal
15 detachment, dry eye and other corneopathies, as well
16 as in the treatment and prevention of various
17 cardiovascular diseases, including, without
18 limitation, diseases associated with lipid
19 metabolism such as dyslipidemias, prevention of
20 post-angioplasty restenosis and as an agent to
21 increase the level of circulating tissue plasminogen
22 activator (TPA). Other uses for retinoid compounds
23 include the prevention and treatment of conditions
24 and diseases associated with human papilloma virus
25 (HPV), including warts and genital warts, various
26 inflammatory diseases such as pulmonary fibrosis,
27 ileitis, colitis and Crohn's disease,
28 neurodegenerative diseases such as Alzheimer's
29 disease, Parkinson's disease and stroke, improper
30 pituitary function, including insufficient
31 production of growth hormone, modulation of
32 apoptosis, including both the induction of apoptosis
33 and inhibition of T-cell activated apoptosis,
34 restoration of hair growth, including combination

1 therapies with the present compounds and other
2 agents such as Minoxidil^R, diseases associated with
3 the immune system, including use of the present
4 compounds as immunosuppressants and
5 immunostimulants, modulation of organ transplant
6 rejection and facilitation of wound healing,
7 including modulation of chelosis.

8 United States Patent Nos. 4,740,519 (Shroot et
9 al.), 4,826,969 (Maignan et al.), 4,326,055
10 (Loeliger et al.), 5,130,335 (Chandraratna et al.),
11 5,037,825 (Klaus et al.), 5,231,113 (Chandraratna et
12 al.), 5,324,840 (Chandraratna), 5,344,959
13 (Chandraratna), 5,130,335 (Chandraratna et al.),
14 Published European Patent Application Nos. 0 170 105
15 (Shudo), 0 176 034 A (Wuest et al.), 0 350 846 A
16 (Klaus et al.), 0 176 032 A (Frickel et al.), 0 176
17 033 A (Frickel et al.), 0 253 302 A (Klaus et al.),
18 0 303 915 A (Bryce et al.), UK Patent Application GB
19 2190378 A (Klaus et al.), German Patent Application
20 Nos. DE 3715955 A1 (Klaus et al.), DE 3602473 A1
21 (Wuest et al., and the articles J. Amer. Acad. Derm.
22 15: 756 - 764 (1986) (Sporn et al.), Chem. Pharm.
23 Bull. 33: 404-407 (1985) (Shudo et al.), J. Med
24 Chem. 1988 31, 2182 - 2192 (Kagechika et al.),
25 Chemistry and Biology of Synthetic Retinoids CRC
26 Press Inc. 1990 p 334 - 335, 354 (Dawson et al.),
27 describe or relate to compounds which include a
28 tetrahydronaphthyl moiety and have retinoid-like or
29 related biological activity.

30 United States Patent Nos. 4,980,369, 5,006,550,
31 5,015,658, 5,045,551, 5,089,509, 5,134,159,
32 5,162,546, 5,234,926, 5,248,777, 5,264,578,
33 5,272,156, 5,278,318, 5,324,744, 5,346,895,
34 5,346,915, 5,348,972, 5,348,975, 5,380,877,

1 5,399,561, 5,407,937, (assigned to the same assignee
2 as the present application) and patents and
3 publications cited therein, describe or relate to
4 chroman, thiochroman and 1,2,3,4-tetrahydroquinoline
5 derivatives which have retinoid-like biological
6 activity.

7 United States Patent No. 4,723,028 (Shudo),
8 Published European Patent Application Nos. 0 170 105
9 (Shudo), German Patent Application No. DE 3524199 A1
10 (Shudo), PCT WO 91/16051 (Spada et al.), PCT WO
11 85/04652 (Polus) and J. Med Chem. 1988 31, 2182 -
12 2192 (Kagechika et al.), describe or relate to aryl
13 and heteroaryl or diaryl substituted olephines or
14 amides having retinoid-like or related biological
15 activity.

16 United States Patent Nos. 4,992,468, 5,013,744,
17 5,068,252, 5,175,185, 5,202,471, 5,264,456,
18 5,324,840, 5,326,898, 5,349,105, 5,391,753,
19 5,414,007 and 5,434,173 (assigned to the same
20 assignee as the present application) and patents and
21 publications cited therein, describe or relate to
22 compounds which have retinoid-like biological
23 activity and a structure wherein a phenyl and a
24 heteroaryl or a phenyl and a second phenyl group is
25 linked with an olephinic or acetylenic linkage.
26 Still further, several co-pending applications and
27 recently issued patents which are assigned to the
28 assignee of the present application, are directed to
29 further compounds having retinoid-like activity.

30 It is now general knowledge in the art that two
31 main types of retinoid receptors exist in mammals
32 (and other organisms). The two main types or
33 families of receptors are respectively designated
34 RARs and RXRs. Within each type there are subtypes;

1 in th RAR family the subtypes are designated RAR_α,
2 RAR_β and RAR_γ, in RXR the subtypes are: RXR_α, RXB_β and
3 RXR_γ. It has also been established in the art that
4 the distribution of the two main retinoid receptor
5 types, and of the several sub-types is not uniform
6 in the various tissues and organs of mammalian
7 organisms.

8 It is also known in the art that the use of
9 retinoid-like compounds for the treatment of various
10 diseases and conditions is not without problems or
11 side effects. The side effects at therapeutic dose
12 levels include headache, teratogenesis,
13 mucocutaneous toxicity, musculoskeletal toxicity,
14 dislipidemias, skin irritation, headache,
15 hepatotoxicity, etc. These side effects limit the
16 acceptability and utility of retinoids for treating
17 disease. Research is still ongoing in the art to
18 determine which of the RAR or RXR families and within
19 each family, which of the subtype or subtypes are
20 responsible for mediating certain therapeutic
21 effects, and which type or subtypes are responsible
22 for mediating one or more of the undesired side
23 effects. Accordingly, among compounds capable of
24 binding to retinoid receptors, specificity or
25 selectivity for one of the main types or families,
26 and even specificity or selectivity for one or more
27 subtypes within a family of receptors, is considered
28 a desirable pharmacological property. Such
29 selectivity or specificity is useful as a research
30 tool for discovering the roles of the several
31 receptor types and subtypes in mediating the various
32 effects of retinoids in biological systems, and also
33 as aid for designing retinoid drugs with specific
34 therapeutic effects and/or with reduced side effects

1 and toxicity. Along these lines, United States
2 Patent No. 5,324,840 describes a class of compounds
3 in which retinoid-like activity is accompanied by
4 reduced skin toxicity and reduced teratogenic
5 effects. United States Patent No. 5,399,586
6 describes the use of compounds having RXR retinoid
7 receptor agonist activity for the treatment of
8 mammals afflicted with tumors. United States Patent
9 No. 5,455,265 describes methods of treatment of
10 mammals with compounds having agonist-like activity
11 on RXR receptors. Published PCT application No.
12 WO93/11755 is also directed to the use of compounds
13 which are selective RXR receptor agonists.

14 The present invention provides methods of
15 treatment of tumors with compounds which are
16 specific or selective to RAR_{α} receptors.

17 **SUMMARY OF THE INVENTION** It has been
18 discovered in accordance with the present invention
19 that retinoid-like compounds which act selectively,
20 or preferably even specifically on RAR_{α} receptor
21 subtypes in preference over RAR_{β} and RAR_{γ} receptor
22 subtypes, possess desirable pharmaceutical
23 properties associated with retinoids, and are
24 particularly suitable for treatment of tumors, such
25 as acute monocytic leukemia, cervical carcinoma,
26 myeloma, ovarian carcinomas and head and neck
27 carcinomas, without having one or more undesirable
28 side effects of retinoids, such as inducement of
29 weight loss, mucocutaneous toxicity, skin irritation
30 and teratogenicity.

31 Accordingly, the present invention relates to
32 the use of RAR_{α} specific or selective retinoid
33 compounds for the treatment of diseases and
34 conditions which respond to treatment by such

1 compounds, and particularly to the treatment of
2 tumors, primarily acute monocytic leukemia, cervical
3 carcinoma, myeloma, ovarian carcinomas and head and
4 neck carcinomas with the RAR_α specific or selective
5 retinoid compounds. In accordance with the present
6 invention the RAR_α selective compounds are also
7 particularly advantageously used for treatment of
8 proliferative vitreoretinopathy (PVR) and age
9 related macular degeneration (AMD).

10 For the purposes of the present description a
11 compound is considered RAR_α specific or selective if
12 in a transactivation assay (described below) the
13 compound transactivates the RAR_α receptors at a
14 significantly lower concentration than the RAR_β and
15 RAR_γ receptors. Instead of measuring
16 transactivation, measuring the binding of a compound
17 respectively to the three RAR receptor subtypes is
18 also feasible. Binding data expressed in Kd numbers
19 obtained in a binding assay (described below) are
20 also indicative of a compound's ability to act
21 specifically or selectively on RAR_α receptors in
22 preference over RAR_β and RAR_γ receptors. A compound
23 is considered RAR_α specific or selective for the
24 purposes of the present invention if the Kd number
25 for its binding to RAR_α receptors is approximately
26 500 times smaller than the Kd for its affinity to
27 RAR_β and RAR_γ receptors.

28 BRIEF DESCRIPTION OF THE DRAWING FIGURES

29 **Figure 1** is a graph showing the results of an RPMI
30 8226 cell culture assay conducted with all trans
31 retinoic acid (ATRA) and two RAR_α selective compounds
32 in accordance with the present invention.

33 **Figure 2** is another graph showing the results of
34 an AML 193 cell culture assay conducted with two RAR_α

1 selective compounds in accordanc with the present
2 invention, and with two compounds which are not RAR_α
3 selective.

4 **Figure 3** is still another graph showing results
5 of an AML 193 cell culture assay conducted with
6 three RAR_α selective compounds in accordance with the
7 present invention and with all trans retinoic acid
8 (ATRA).

9 **Figure 4** is a graph showing the proliferation of
10 ovarian tumor cells in a cell culture assay (EDR
11 assay) in the presence of varying concentrations of
12 **Compound 2** in accordance with the present invention.

13 **Figure 5** is a graph showing the RPE cell
14 proliferation in the presence of all trans retinoic
15 acid or **Compound 42** in the culture medium.

16 **Figure 6** is a graph showing the weight of a
17 group of experimental rats which were administered
18 for 3 days varying doses of an RAR_α selective
19 compound in accordance with the present invention.

20 **Figure 7** is a bar graph showing the weight of
21 a group of experimental rats at the end of a 4 day
22 period wherein for three days the rats were
23 administered varying doses of **Compound 18** in
24 accordance with the invention;

25 **Figure 8** is a graph showing the weight of guinea
26 pigs which were treated with varying doses of
27 **Compound 42** for 15 days.

28 **DETAILED DESCRIPTION OF THE INVENTION**General
29 EmbodimentsDefinitions regarding the chemical
30 compounds used in the present invention

31 The term alkyl refers to and covers any and all
32 groups which are known as normal alkyl,
33 branched-chain alkyl and cycloalkyl. The term
34 alkenyl refers to and covers normal alkenyl, branch

1 chain alkenyl and cycloalkenyl groups having one or
2 more sites of unsaturation. Similarly, the term
3 alkynyl refers to and covers normal alkynyl, and
4 branch chain alkynyl groups having one or more
5 triple bonds.

6 Lower alkyl means the above-defined broad
7 definition of alkyl groups having 1 to 6 carbons in
8 case of normal lower alkyl, and as applicable 3 to 6
9 carbons for lower branch chained and cycloalkyl
10 groups. Lower alkenyl is defined similarly having 2
11 to 6 carbons for normal lower alkenyl groups, and 3
12 to 6 carbons for branch chained and cyclo- lower
13 alkenyl groups. Lower alkynyl is also defined
14 similarly, having 2 to 6 carbons for normal lower
15 alkynyl groups, and 4 to 6 carbons for branch
16 chained lower alkynyl groups.

17 The term "ester" as used here refers to and
18 covers any compound falling within the definition of
19 that term as classically used in organic chemistry.
20 It includes organic and inorganic esters. Where B
21 in the general formula of the preferred compounds
22 used in the invention is -COOH , this term covers the
23 products derived from treatment of this function
24 with alcohols or thioalcohols preferably with
25 aliphatic alcohols having 1-6 carbons. Where the
26 ester is derived from compounds where B is $\text{-CH}_2\text{OH}$,
27 this term covers compounds derived from organic
28 acids capable of forming esters including
29 phosphorous based and sulfur based acids, or
30 compounds of the formula $\text{-CH}_2\text{OCOR}_{11}$ where R_{11} is any
31 substituted or unsubstituted aliphatic, aromatic,
32 heteroaromatic or aliphatic aromatic group,
33 preferably with 1-6 carbons in the aliphatic
34 portions.

1 Unless stated otherwise in this application,
2 preferred esters are derived from the saturated
3 aliphatic alcohols or acids of ten or fewer carbon
4 atoms or the cyclic or saturated aliphatic cyclic
5 alcohols and acids of 5 to 10 carbon atoms.
6 Particularly preferred aliphatic esters are those
7 derived from lower alkyl acids and alcohols. Also
8 preferred are the phenyl or lower alkyl phenyl
9 esters.

10 Amides has the meaning classically accorded that
11 term in organic chemistry. In this instance it
12 includes the unsubstituted amides and all aliphatic
13 and aromatic mono- and di- substituted amides.
14 Unless stated otherwise in this application,
15 preferred amides are the mono- and di-substituted
16 amides derived from the saturated aliphatic radicals
17 of ten or fewer carbon atoms or the cyclic or
18 saturated aliphatic-cyclic radicals of 5 to 10
19 carbon atoms. Particularly preferred amides are
20 those derived from substituted and unsubstituted
21 lower alkyl amines. Also preferred are mono- and
22 disubstituted amides derived from the substituted
23 and unsubstituted phenyl or lower alkylphenyl
24 amines. Unsubstituted amides are also preferred.

25 Acetals and ketals include the radicals of the
26 formula-CK where K is $(-OR)_2$. Here, R is lower
27 alkyl. Also, K may be $-OR_2O-$ where R₂ is lower alkyl
28 of 2-5 carbon atoms, straight chain or branched.

29 A pharmaceutically acceptable salt may be
30 prepared for any compound used in this invention
31 having a functionality capable of forming such-salt,
32 for example an acid functionality. A
33 pharmaceutically acceptable salt is any salt which
34 retains the activity of the parent compound and does

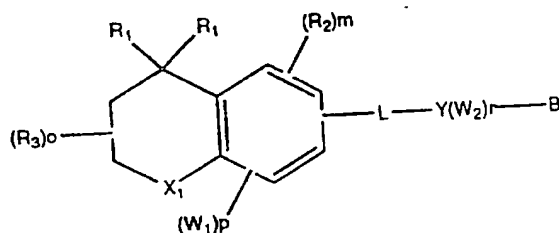
1 not impart any deleterious or untoward effect on the
2 subject to which it is administered and in the
3 context in which it is administered.
4 Pharmaceutically acceptable salts may be derived
5 from organic or inorganic bases. The salt may be a
6 mono or polyvalent ion. Of particular interest are
7 the inorganic ions, sodium, potassium, calcium, and
8 magnesium. Organic salts may be made with
9 amines, particularly ammonium salts such as mono-,
10 di- and trialkyl amines or ethanol amines. Salts
11 may also be formed with caffeine, tromethamine and
12 similar molecules. Where there is a nitrogen
13 sufficiently basic as to be capable of forming acid
14 addition salts, such may be formed with any
15 inorganic or organic acids or alkylating agent such
16 as methyl iodide. Preferred salts are those formed
17 with inorganic acids such as hydrochloric acid,
18 sulfuric acid or phosphoric acid. Any of a number
19 of simple organic acids such as mono-, di- or tri-
20 acid may also be used.

21 Some of the compounds used in the present
22 invention may have trans and cis (E and Z) isomers.
23 In addition, the compounds used in the present
24 invention may contain one or more chiral centers and
25 therefore may exist in enantiomeric and
26 diastereomeric forms. The scope of the present
27 invention is intended to cover the use of all such
28 isomers per se, as well as mixtures of cis and trans
29 isomers, mixtures of diastereomers and racemic
30 mixtures of enantiomers (optical isomers) as well.
31 Description of the Compounds Preferably Used in the
32 Methods of the Invention

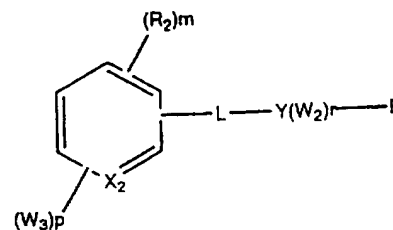
33 The retinoid-like compounds used in the methods
34 of treatment of the present invention are specific

1 or selective for RAR_α receptors. That a compound is
 2 specific or selective to RAR_α receptors can be
 3 ascertained in transactivation assays described
 4 below where an RAR_α specific or selective compound
 5 transactivates RAR_α receptors at a significantly
 6 lower concentrations than RAR_β or RAR_γ receptors. In
 7 a binding assay where the ability of the compound to
 8 bind to these receptor subtypes is measured, a
 9 compound that is considered RAR_α specific or
 10 selective for the purposes of the present invention
 11 binds at least approximately 500 times stronger to
 12 RAR_α receptors than to the RAR_β or RAR_γ receptors.
 13 Alternatively, the compound is considered RAR_α
 14 specific or selective if in the binding assay its K_d
 15 number is approximately in the 10^{-1} to 5×10^2
 16 nanomolar range and the K_d number for RAR_β or RAR_γ
 17 receptors is greater than 1000 nanmolar. The latter
 18 is indicated by 0.00 in the below provided Tables
 19 where binding data (K_d numbers) for certain
 20 exemplary compounds of the present invention are
 21 illustrated.

22 Examples for RAR_α selective compounds which are
 23 preferably used in accordance with the present
 24 invention are illustrated by Formula 1 and Formula 2



34 Formula 1



Formula 2

1 where X_1 is 0 or X_1 is $[C(R_1)_m]_n$ where m is an integer
2 between 0 and 2;

3 R_1 is independently H or alkyl of 1 to 6
4 carbons;

5 R_2 is independently hydrogen, or lower alkyl of
6 1 to 6 carbons;

7 R_3 is hydrogen, lower alkyl of 1 to 6 carbons or
8 F;

9 m is an integer having the value of 0 - 5;

10 n is an integer having the value of 0 - 4;

11 p is an integer having the value of 0 - 2;

12 r is an integer having the value 0 - 2;

13 X_2 is N or CH;

14 Y is a phenyl or naphthyl group, or heteroaryl
15 selected from a group consisting of pyridyl,
16 thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
17 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said
18 phenyl, naphthyl and heteroaryl groups being
19 optionally substituted with one or two R_2 groups;

20 W_1 is a substituent selected independently from
21 the group consisting of F, Br, Cl, I, fluoro
22 substituted C_{1-6} alkyl, NO_2 , and OH, with the provisos
23 that:

24 (i) when the compound is in accordance with
25 Formula 1 and Z is 0 then the sum of p and r is at
26 least 1 and W_1 is not a fluoro group in the 3
27 position of a tetrahydronaphthalene ring;

28 (ii) when the compound is in accordance with
29 Formula 1 and r is zero and p is 1 and W_1 is OH then
30 the OH group is positioned α to the L group;

31 W_2 is a substituent selected independently from
32 the group consisting of F, Br, Cl, I, fluoro
33 substituted C_{1-6} alkyl, NO_2 , and OH;

34 W_3 is a substituent selected independently from

1 the group consisting of F, Br, Cl, I, C₁₋₆alkyl,
2 fluoro substituted C₁₋₆ alkyl, NO₂, and OH with the
3 proviso that when the compound is in accordance with
4 Formula 2 and X₂ is CH and r is 0 then p is not 0 and
5 at least one W₁ group is not alkyl;

6 L is -(C=Z)-NH- or -NH-(C=Z)-

7 Z is O or S, and

8 B is COOH or a pharmaceutically acceptable salt
9 thereof, COOR₈, CONR₈R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁,
10 CHO, CH(OR₁₂)₂, CHOR₁₃O, -COR₇, CR₇(OR₁₂)₂, CR₇OR₁₃O,
11 where R₇ is an alkyl, cycloalkyl or alkenyl group
12 containing 1 to 5 carbons, R₈ is an alkyl group of 1
13 to 10 carbons or trimethylsilylalkyl where the alkyl
14 group has 1 to 10 carbons, or a cycloalkyl group of
15 5 to 10 carbons, or R₈ is phenyl or lower
16 alkylphenyl, R₉ and R₁₀ independently are hydrogen,
17 an alkyl group of 1 to 10 carbons, or a cycloalkyl
18 group of 5-10 carbons, or phenyl or lower
19 alkylphenyl, R₁₁ is lower alkyl, phenyl or lower
20 alkylphenyl, R₁₂ is lower alkyl, and R₁₃ is divalent
21 alkyl radical of 2-5 carbons.

22 With reference to symbol X₁ in Formula 1,
23 compounds are preferred in the methods of the
24 present invention where X₁ is [C(R₁)₂]_n and n is 1
25 (tetrahydronaphthalene derivatives) and also where X₁
26 is O (chroman derivatives). With reference to the
27 symbol X₂ in Formula 2, compounds are equally
28 preferred where X₂ is CH or N. When X₂ is CH then
29 the benzene ring is preferably 1, 3, 5 substituted
30 with the L group occupying the 1 position and the W₁
31 and/or R₂ groups occupying the 3 and 5 positions.
32 When the symbol X₂ is N, then the pyridine ring is
33 preferably 2,4,6 substituted with the L group
34 occupying the 4 position and the W₁ and/or R₂ groups

1 occupying the 2 and 6 positions.

2 The R_1 groups of Formula 1 are preferably H or
3 CH_3 . The R_2 group of Formula 1 is preferably H. The
4 group B of the preferred compounds of the invention
5 is COOH or a pharmaceutically acceptable salt
6 thereof, COOR_9 or $\text{CONR}_9\text{R}_{10}$, where R_9 , R_9 , and R_{10} are
7 defined as above.

8 Referring now to the W_1 and W_2 groups in Formula
9 1, these groups are, generally speaking, electron
10 withdrawing groups, which are present in the
11 compounds of the invention either in the aromatic
12 portion of the condensed ring system, or as a
13 substituent of the aryl or heteroaryl group Y.
14 Preferably a W_2 group is present in the Y group, and
15 a W_1 group is also present in the aromatic portion of
16 the condensed ring system. When the Z group is S
17 (thioamides) a W_1 or W_2 group does not necessarily
18 have to be present in the compounds of the invention
19 in accordance with Formula 1, although preferably
20 at least one of the W_1 or W_2 groups is nevertheless
21 present. In the aryl or heteroaryl Y moiety in the
22 compounds of Formula 1 and Formula 2 as well, the W_2
23 group is preferably located in the position adjacent
24 to the B group; preferably the B group is in para
25 position in the phenyl ring relative to the "amide"
26 moiety, and therefore the W_2 group is preferably in
27 meta position relative to the amide moiety. Where
28 there is a W_1 group present in the aromatic portion
29 of the condensed ring system of the compounds of
30 Formula 1, it preferably occupies the 8 position of
31 the chroman nucleus with the $\text{Z}=\text{C}-\text{NH}-$ group occupying
32 the 6 position. In tetrahydronaphthalene compounds
33 of Formula 1, the $\text{Z}=\text{C}-\text{NH}-$ group is preferably in the
34 2-position, and the W_1 group is preferably in the 4

1 position. However, when the W_1 group is OH in
2 compounds of Formula 1, then the OH is preferably in
3 the 3 position of the tetrahydronaphthalene ring.

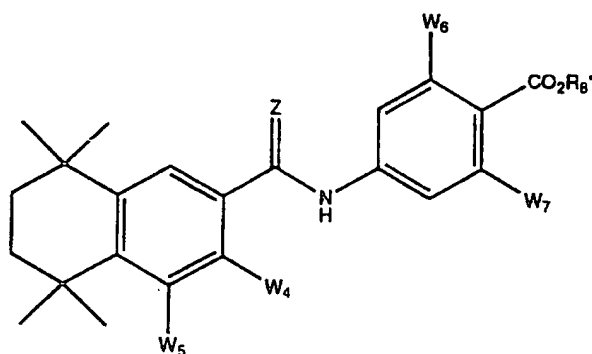
4 Preferred W_1 and W_2 groups are F, NO_2 , Br, I,
5 CF_3 , ClN_3 , and OH. The presence of one or two
6 fluoro substituents in the Y group (W_2) is especially
7 preferred. When the Y group is phenyl, the fluoro
8 substituents preferably are in the ortho and ortho'
9 positions relative to the B group, which is
10 preferably COOH or $COOR_s$.

11 Referring now to the W_3 group in Formula 2, this
12 group is, generally speaking, also an electron
13 withdrawing group or an alkyl group, more
14 specifically preferred W_3 groups are F, NO_2 , Br, I,
15 CF_3 , N_3 , and OH. Alternatively, in the phenyl or
16 pyridyl ring (shown in Formula 2 as substituent
17 " $(W_3)_p$ ") W_3 is an alkyl group, preferably
18 branch-chained alkyl, such as tertiary butyl, and
19 preferably p is 2.

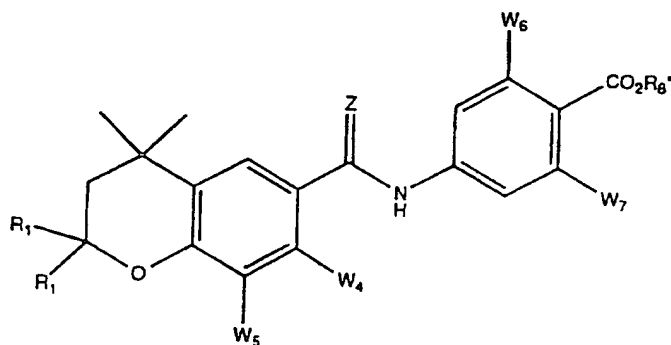
20 With reference to the symbol Y in Formula 1 and
21 in Formula 2 as well, the preferred compounds used
22 in the methods of the invention are those where Y is
23 phenyl, pyridyl, 2-thiazolyl, thienyl, or furyl,
24 more preferably phenyl. As far as substitutions on
25 the Y (phenyl) and Y (pyridyl) groups are concerned,
26 compounds are preferred where the phenyl group is
27 1,4 (para) substituted by the L and B groups, and
28 where the pyridine ring is 2,5 substituted by the L
29 and B groups. (Substitution in the 2,5 positions in
30 the "pyridine" nomenclature corresponds to
31 substitution in the 6-position in the "nicotinic
32 acid" nomenclature.) In the preferred compounds of
33 the invention there is no optional R_1 substituent
34 (other than H) on the Y group.

1 Th L group of Formula 1 and of Formula 2 is
2 preferably $-(C=Z)-NH-$, and Z is preferably O. In
3 other words, those carbamoyl or amide compounds are
4 preferred in accordance with the present invention
5 where the $-NH$ -moiety is attached to the Y group.

6 The compounds which are presently most
7 preferably used in the methods of treatment of the
8 invention are shown below in Table 1 with reference
9 to Formulas 3 and 4 and in Table 2 with reference
10 to Formula 5.



Formula 3



Formula 4

Formula 5

TABLE 1

Compound

No.	Formula	R ₁ [°]	W ₄	W ₅	Z	W ₆	W ₇	RS [°]
1	3	--	H	H	O	F	H	Et
2	3	--	H	H	O	F	H	H
3	3	--	H	Br	O	F	H	Et
4	3	--	H	Br	O	F	H	H
5	3	--	OH	H	O	F	H	Et
6	3	--	OH	H	O	F	H	H
7	4	H	H	Br	O	F	H	Et
8	4	H	H	Br	O	F	H	H
9	4	CH ₃	H	Br	O	F	H	Et
10	4	CH ₃	H	Br	O	F	H	H
11	4	CH ₃	H	CF ₃	O	F	H	Et
12	4	CH ₃	H	CF ₃	O	F	H	H
13	4	CH ₃	H	N ₃	O	F	H	Et
14	4	CH ₃	H	N ₃	O	F	H	H
15	4	CH ₃	H	CF ₃	O	F	F	CH ₃
16	4	CH ₃	H	CF ₃	O	F	F	H
17	4	CH ₃	H	I	O	F	H	Et
18	4	CH ₃	H	I	O	F	H	H
19	4	CH ₃	H	CH ₃	O	F	H	Et
20	4	CH ₃	H	CH ₃	O	F	H	H
21	3	--	H	H	S	H	H	Et
22	3	--	H	H	S	H	H	H
23	3	--	H	H	S	F	H	Et

19

1	24	3	--	H	H	S	F	H	H
2	25	3	--	H	Br	O	NO ₂	H	CH ₃
3	26	3	--	H	Br	O	NO ₂	H	H
4	27	4	CH ₃	H	H	O	F	H	Et
5	28	4	CH ₃	H	H	O	F	H	H
6	29	3	--	OH	Br	O	F	H	Et
7	30	3	--	OH	Br	O	F	H	H
8	31	3	--	OH	Br	O	F	F	Me
9	32	3	--	OH	Br	O	F	F	H
10	33	3	--	H	H	O	F	F	Me
11	34	3	--	H	H	O	F	F	H

Table 2

14	Compound #	X ₂	W ₈	W ₉	W ₁₀	R ₁₁
15	41	N	H	F	H	Et
16	42	N	H	F	H	H
17	43	N	H	H	H	Et
18	44	N	H	H	H	H
19	45	CH	H	F	H	Et
20	46	CH	H	F	H	H
21	47	CH	OH	F	H	Et
22	48	CH	OH	F	H	H
23	49	N	H	F	F	Me
24	50	N	H	F	F	H
25	51	CH	H	F	F	Me
26	52	CH	H	F	F	H
27	53	N	H	NO ₂	H	Me
28	54	N	H	NO ₂	H	H

Modes of Administration

The RAR₁ specific or selective compounds used in the methods of this invention may be administered systemically or topically, depending on such considerations as the condition to be treated, need

1 for site-specific treatment, quantity of drug to be
2 administered, and numerous other considerations.

3 In the treatment of dermatoses, it will
4 generally be preferred to administer the drug
5 topically, though in certain cases such as treatment
6 of severe cystic acne or psoriasis, oral
7 administration may also be used. Any common topical
8 formulation such as a solution, suspension, gel,
9 ointment, or salve and the like may be used.

10 Preparation of such topical formulations are well
11 described in the art of pharmaceutical formulations
12 as exemplified, for example, Remington's
13 Pharmaceutical Science, Edition 17, Mack Publishing
14 Company, Easton, Pennsylvania. For topical
15 application, these compounds could also be
16 administered as a powder or spray, particularly in
17 aerosol form. If the drug is to be administered
18 systemically, it may be confected as a powder, pill,
19 tablet or the like or as a syrup or elixir suitable
20 for oral administration. For intravenous or
21 intraperitoneal administration, the compound will be
22 prepared as a solution or suspension capable of
23 being administered by injection. In certain cases,
24 it may be useful to formulate these compounds by
25 injection. In certain cases, it may be useful to
26 formulate these compounds in suppository form or as
27 extended release formulation for deposit under the
28 skin or intramuscular injection.

29 Other medicaments can be added to such topical
30 formulation for such secondary purposes as treating
31 skin dryness; providing protection against light;
32 other medications for treating dermatoses;
33 medicaments for preventing infection, reducing
34 irritation, inflammation and the like.

1 Treatment of dermatoses or any other indications
2 known or discovered to be susceptible to treatment
3 by retinoic acid-like compounds will be effected by
4 administration of the therapeutically effective dose
5 of one or more compounds of the instant invention.
6 A therapeutic concentration will be that
7 concentration which effects reduction of the
8 particular condition, or retards its expansion. In
9 certain instances, the compound potentially may be
10 used in prophylactic manner to prevent onset of a
11 particular condition.

12 A useful therapeutic or prophylactic
13 concentration will vary from condition to condition
14 and in certain instances may vary with the severity
15 of the condition being treated and the patient's
16 susceptibility to treatment. Accordingly, no single
17 concentration will be uniformly useful, but will
18 require modification depending on the
19 particularities of the disease being treated. Such
20 concentrations can be arrived at through routine
21 experimentation. However, it is anticipated that in
22 the treatment of, for example, acne, or similar
23 dermatoses, that a formulation containing between
24 0.01 and 1.0 milligrams per milliliter of formulation
25 will constitute a therapeutically effective
26 concentration for total application. If
27 administered systemically, an amount between 0.01
28 and 5 mg per kg per day of body weight would be
29 expected to effect a therapeutic result in the
30 treatment of many diseases for which these compounds
31 are useful.

32 In the treatment of tumors a dose of
33 approximately 0.5 to 5 mg per kg body weight per day
34 is anticipated to constitute the therapeutic dose.

1 Alternatively, as is performed frequently in therapy
2 of malignancies, a patient is provided an initial
3 dose of 1 mg per kg body weight per day, and
4 thereafter the dose is raised until a maximum
5 tolerated dose is attained.

6 Assay of RAR_α receptor selective biological activity
7 and its significance in reduced side effects and
8 toxicity

9 As it is noted in the introductory section of
10 this application for patent two main types of
11 retinoic acid receptors (RAR and RXR) exist in
12 mammals (and other organisms). Within each type
13 there are sub-types (RAR_α, RAR_β, RAR_γ, RXR_α, RXR_β and
14 RXR_γ) the distribution of which is not uniform in the
15 various tissues and organs of mammalian organisms.
16 Selective binding of only one or two retinoid
17 receptor subtypes within one retinoid receptor
18 family can give rise to beneficial pharmacological
19 properties because of the varying distribution of
20 the sub-types in the several mammalian tissues or
21 organs. For the above-summarized reasons, binding
22 of any or all of the retinoid receptors, as well as
23 specific or selective activity in a receptor family,
24 or selective or specific activity in any one of the
25 receptor subtypes, are all considered desirable
26 pharmacological properties.

27 In light of the foregoing the prior art has
28 developed assay procedures for testing the agonist
29 like activity of compounds in the RAR_α, RAR_β, RAR_γ,
30 RXR_α, RXR_β and RXR_γ receptor subtypes. For example,
31 a chimeric receptor transactivation assay which
32 tests for agonist-like activity in the RAR_α, RAR_β,
33 RAR_γ, and RXR_α receptor subtypes, and which is based
34 on work published by Feigner P. L. and Holm M.

1 (1989) Focus, 11 2 is described in detail in U.S.
2 Patent No. 5,455,265. The specification of United
3 States Patent No. 5,455,265 is expressly
4 incorporated herein by reference.

5 A holoreceptor transactivation assay and a
6 ligand binding assay which measure the ability of
7 compounds to bind to the several retinoid receptor
8 subtypes, respectively, are described in published
9 PCT Application No. WO WO93/11755 (particularly on
10 pages 30 - 33 and 37 - 41) published on June 24,
11 1993, the specification of which is also
12 incorporated herein by reference. A description of
13 the ligand binding assay is also provided below.

14 BINDING ASSAY

15 All binding assays were performed in a similar
16 fashion. All six receptor types were derived from
17 the expressed receptor type (RAR α , β , γ and RXR α ,
18 β , γ) expressed in Baculovirus. Stock solutions of
19 all compounds were prepared as 10mM ethanol
20 solutions and serial dilutions carried out into 1:1
21 DMSO; ethanol. Assay buffers consisted of the
22 following for all six receptor assays: 8% glycerol,
23 120mM KCl, 8mM Tris, 5mM CHAPS 4mM DTT and 0.24mM
24 PMSF, pH - 7.4@ room temperature.

25 All receptor binding assays were performed in
26 the same manner. The final assay volume was 250 μ l
27 and contained from 10-40 μ g of extract protein
28 depending on receptor being assayed along with 5 nM
29 of [3 H] all-trans retinoic acid or 10nM [3 H] 9-cis
30 retinoic acid and varying concentrations of
31 competing ligand at concentrations that ranged from
32 0 - 10^{-5} M. The assays were formatted for a 96 well
33 minitube system. Incubations were carried out at
34 4°C until equilibrium was achieved. Non-specific

1 binding was defined as that binding remaining in the
2 presence of 1000nM of the appropriate unlabeled
3 retinoic acid isomer. At the end of the incubation
4 period, 50 μ l of 6.25% hydroxyapatite was added in
5 the appropriate wash buffer. The wash buffer
6 consisted of 100mM KCl, 10mM Tris and either 5mM
7 CHAPS (RXR α , β , γ) or 0.5% Triton X-100 (RAR α , β ,
8 γ). The mixture was vortexed and incubated for 10
9 minutes at 4°C, centrifuged and the supernatant
10 removed. The hydroxyapatite was washed three more
11 times with the appropriate wash buffer. The
12 receptor-ligand complex was adsorbed by the
13 hydroxyapatite. The amount of receptor-ligand
14 complex was determined by liquid scintillation
15 counting of hydroxyapatite pellet.

16 After correcting for non-specific binding, IC₅₀
17 values were determined. The IC₅₀ value is defined as
18 the concentration of competing ligand needed to
19 reduce specific binding by 50%. The IC₅₀ value was
20 determined graphically from a loglogit plot of the
21 data. The K_d values were determined by application
22 of the Cheng-Prusoff equation to the IC₅₀ values, the
23 labeled ligand concentration and the K_d of the
24 labeled ligand.

25 The results of ligand binding assay are expressed
26 in K_d numbers. (See Cheng et al. Biochemical
27 Pharmacology Vol. 22 pp 3099-3108, expressly
28 incorporated herein by reference.)

29 Table 3 shows the results of the ligand binding
30 assay for certain exemplary compounds of the
31 invention.

TABLE 3

Ligand Binding Assay

Compound #	K _d (nanomolar)					
	RAR α	RAR β	RAR γ	RXR α	RXR β	RXR γ
2	1.90	480.0	0.00	0.00	0.00	0.00
4	1.3	0.00	0.00	0.00	0.00	0.00
6	3.00	0.00	0.00	0.00	0.00	0.00
10	24.0	0.00	0.00	0.00	0.00	0.00
12	14.0	0.00	0.00	0.00	0.00	0.00
14	52.0	0.00	0.00	0.00	0.00	0.00
16	51.0	0.00	0.00	0.00	0.00	0.00
18	16.0	0.00	0.00	0.00	0.00	0.00
20	57.0	0.00	0.00	0.00	0.00	0.00
22	15	0.00	0.00	0.00	0.00	0.00
24	7.5	0.00	0.00	0.00	0.00	0.00
26	245.0	0.00	0.00	0.00	0.00	0.00
28	162.0	0.00	0.00	0.00	0.00	0.00
30	<3.00	0.00	0.00	0.00	0.00	0.00
32	2.30	0.00	0.00	0.00	0.00	0.00
34	9.00	0.00	0.00	0.00	0.00	0.00
42	14.00	0.00	0.00	0.00	0.00	0.00
44	19.00	0.00	0.00	0.00	0.00	0.00
46	26.0	0.00	0.00	0.00	0.00	0.00
48	77.0	0.00	0.00	0.00	0.00	0.00
50	62.0	0.00	0.00	0.00	0.00	0.00
52	87.0	0.00	0.00	0.00	0.00	0.00
54	94.0	0.00	0.00	0.00	0.00	0.00
TTNPB ¹ 72		5		36		

0.00 indicates value greater than 1000nM (nanomolar)

¹ TTNPB is a well known prior art retinoid (4-(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)propen-1-yl)benzoic acid, that is not RAR α selective.

1 As it can be seen from the foregoing data, the
2 compounds used in accordance with the present
3 invention specifically or selectively bind to RAR_α
4 retinoid receptors. It has been discovered in
5 accordance with the present invention that this
6 unique type of selectivity allows the compounds to
7 retain beneficial retinoid-like properties while
8 reduces certain side effects and toxicity. More
9 specifically, certain in vitro cell culture assays
10 are described below, in which the ability of the RAR_α
11 specific or selective compounds to significantly
12 inhibit the growth of cancer cells is demonstrated.

13 CANCER CELL LINE ASSAYS

14 MATERIALS AND METHODS

15 Hormones

16 All trans-retinoic acid (t-RA) (Sigma Chemicals
17 Co., St. Louis, MO) was stored at -70°C. Prior to
18 each experiment the compound was dissolved in 100%
19 ethanol at 1 mM and diluted in culture medium
20 immediately before use. All experiments were
21 performed in subdued light. Controls were assayed
22 using the same concentration of ethanol as present
23 in the experimental plates and this concentration of
24 diluent had no effect in either assay.

25 Cells and Cell Culture

26 The cell lines, RPMI 8226, ME-180 and AML-193
27 were obtained from the American Type Culture
28 Collection (ATCC, Rockville, MD). RPMI 8226 is a
29 human hematopoietic cell line obtained from the
30 peripheral blood of a patient with multiple myeloma.
31 The cells resemble the lymphoblastoid cells of other
32 human lymphocyte cell lines and secrete α-type light
33 chains of immunoglobulin. RPMI-8226 cells are grown
34 in RPMI medium (Gibco) supplemented with 10% fetal

1 bovine serum, glutamine and antibiotics. Th cells
2 were maintained as suspension cultures grown at 37°C
3 in a humidified atmosphere of 5% CO₂ in air. The
4 cells were diluted to a concentration of 1 x 10⁵/ml
5 twice a week.

6 ME-180 is a human epidermoid carcinoma cell line
7 derived from the cervix. The tumor was a highly
8 invasive squamous cell carcinoma with irregular cell
9 clusters and no significant keratinization. ME-180
10 cells were grown and maintained in McCoy's 5a medium
11 (Gibco) supplemented with 10% fetal bovine serum,
12 glutamine and antibiotics. The cells were
13 maintained as monolayer cultures grown at 37°C in a
14 humidified atmosphere of 5% CO₂ in air. The cells
15 were diluted to a concentration of 1 x 10⁵/ml twice a
16 week.

17 AML-193 was established from the blast cells
18 classified as M5 Acute Monocyte Leukemia. The
19 growth factor, granulocyte colony-stimulation factor
20 (GM-CSF) was required to establish this cell line
21 and growth factors are necessary for its continuous
22 proliferation in chemically defined medium. AML-193
23 cells were grown and maintained in Iscove's modified
24 Dulbecco's medium supplemented with 10% fetal bovine
25 serum, glutamine and antibiotics with 5µg/ml insulin
26 (Sigma Chemical Co.) and 2 ng/ml rh GM-CSF (R and D
27 Systems). The cells were diluted to a concentration
28 of 3 x 10⁵/ml twice a week.

29 Incorporation of ³H-Thymidine

30 The method used for determination of the
31 incorporation of radiolabeled thymidine was adapted
32 from the procedure described by Shrivastav et al.
33 RPMI-8226 cells were plated in a 96 well round
34 bottom microtiter plate (Costar) at a density of

1 1,000 cells/w ll. To appropriat wells, retinoid
2 test compounds were added at the final
3 concentrations indicated for a final volume of 150
4 μ l/well. The plates were incubated for 96 hours at
5 37°C in a humidified atmosphere of 5% CO₂ in air.
6 Subsequently, 1 μ Ci of [5'-³H]-thymidine (Amersham,
7 U.K. 43 Ci/mmol specific activity) in 25 μ l culture
8 medium was added to each well and the cells were
9 incubated for an additional 6 hours. The cultures
10 were further processed as described below.

11 ME-180 wells, harvested by trypsinization were
12 plated in a 96 well flat bottom microtiter plate
13 (Costar) at a density of 2,000 cells/well. The
14 cultures were treated as described above for RPMI
15 8226 with the following exceptions. After
16 incubation with thymidine the supernatant was
17 carefully removed, and the cells were washed with a
18 0.5 mM solution of thymidine in phosphate buffered
19 saline. ME180 cells were briefly treated with 50 μ l
20 of 2.5% trypsin to dislodge the cells from the
21 plate.

22 AML-193 cells were plated in a 96 well round
23 bottom microtiter plate (Costar) at a density of
24 1,000 cells/well. To appropriate wells, retinoid
25 test compounds were added at the final
26 concentrations indicated for a final volume of 150
27 μ l/well. The plates were incubated for 96 hours at
28 37°C in a humidified atmosphere of 5% CO₂ in air.
29 Subsequently, 1 μ Ci of [5'-³H]-thymidine (Amersham,
30 U.K., 43 Ci/mmol specific activity) in 25 μ l culture
31 medium was added to each well and the cells were
32 incubated for an additional 6 hours.

33 The cell lines were then processed as follows:
34 the cellular DNA was precipitated with 10%

1 trichloroacetic acid onto glass fiber filter mats
2 using a SKATRON multi-well cell harvester (Skatron
3 Instruments, Sterling VA). Radioactivity
4 incorporated into DNA, as a direct measurement of
5 cell growth, was measured by liquid scintillation
6 counting. The numbers represent the mean
7 disintegrations per minute of incorporated thymidine
8 from triplicate wells \pm SEM.

9 The graph of Figure 1 of the appended drawings
10 shows that in the above described RPMI 8226 cell
11 (malignant myeloma) culture assay Compounds 4 and 12
12 (two exemplary compounds used in accordance with
13 this invention) inhibited the growth of these
14 malignant cells, substantially as well as a
15 comparison compound, all trans retinoic acid (ATRA).
16 The graph of Figure 1 also demonstrates that whereas
17 in a low concentration range (10^{-12} to approximately
18 10^{-9}) all trans retinoic acid (ATRA) actually
19 facilitates growth of these cells, the RAR_{α} selective
20 Compounds 4 and 12 of the present invention do not
21 stimulate but rather already in this low
22 concentrations inhibit the growth of these malignant
23 cells.

24 The graph of Figure 2 shows that in the above
25 described AML 193 (acute monocytic leukemia) cell
26 culture assay Compounds 22 and 42 in accordance with
27 this invention inhibited the growth of these
28 malignant cells. Two other compounds for which data
29 are also shown in this graph are designated AGN
30 193090 and AGN 193459. (An AGN number is an
31 arbitrary designation number used by the corporate
32 assignee of the present invention.) The compounds
33 AGN 193090 and AGN 193459 are not RAR_{α} selective.
34 These compounds respectively are

1 4-[(8-cyano-5,6-dihydro-5,5-dimethylnaphth-2-yl)ethy
2 nyl]benzoic acid, and
3 4-[(5,6-dihydro-5,5-dimethylnaphth-7(6H)-8-(1-2,2-di
4 methylpropylidene)naphth-2-yl)ethynyl]benzoic acid,
5 and their Kd values for RAR α , RAR β , and RAR γ receptors
6 are 109, 34, 77 and 6, 2, 7, respectively. The
7 graph of Figure 2 demonstrates that the RAR α
8 selective or specific compounds inhibit the
9 malignant cell growth at low concentrations where
10 the pan agonist AGN 193090 and AGN 193459 compounds
11 do not inhibit but rather at these low
12 concentrations even stimulate such cell growth.

13 Figure 3 is another graph showing the results of
14 an AML-193 cell culture assay, where Compounds 4, 12
15 and 18 in accordance with the present invention, and
16 all trans retinoic acid (ATRA) were tested. The
17 data show that the RAR α selective compounds reduce
18 cell proliferation at low concentrations whereas
19 ATRA at the same low concentration actually promotes
20 cell proliferation.

21 In another line of assays the effect of the
22 retinoid compounds is tested against cells obtained
23 from solid tumors of patients. This EDR assay is
24 described below as follows:

25 Freshly resected solid tumor biopsies were
26 received within 24 hours of surgery. Species were
27 processed for assay after retaining a portion of the
28 tumor for paraffin embedding and histopathologic
29 confirmation of specimen viability and tissue
30 diagnosis. The remaining specimen was dissociated
31 into small fragments using sterile scissors. The
32 small tissue fragments were then exposed to
33 collagenase and DNAase for 2 hours with mixing a CO $_2$
34 incubator in order to release the tumor cells from

1 the connectiv tissue stroma. The resulting cell
2 suspension was washed, and cell counts determined
3 from a cytopsin preparation. Tumor cells were
4 resuspended at 40,000 cells per ml in 0.3% agarose
5 in RMPI 1640 supplemented with 15% FCS, glutamine
6 and antibiotics, and 0.5 ml were plated into each
7 well of a 24 well plate over 0.5 ml layer of 0.5%
8 agarose. These culture conditions prevent cell
9 adherence, thereby allowing only transformed cells
10 to proliferate. Additionally, the cells grow into
11 three dimensional spheroids, recapitulating their in
12 vivo morphology.

13 Retinoid drugs were added 24 hours after plating
14 to insure specimen reequilibration to a growth
15 environment after the rigors of transport and
16 processing. Cells were grown for four days in the
17 presence of drug, with ³H-thymidine (5 uCi/ml) added
18 48 hours prior to harvest to insure adequate
19 labeling of proliferating cells. After the
20 agarose-cell suspension was liquefied at 90°C, cells
21 were harvested onto glass fiber filters, which were
22 counted in 5 ml scintillation fluid using a Beckman
23 6500 liquid scintillation counter.

24 Results are reported as fraction of untreated
25 control cell proliferation. Treatment groups were
26 performed in duplicate or triplicate, while the
27 controls were performed in quadruplicate.

28 The graph of Figure 4 shows the effect of
29 Compound 2 on ovarian tumors obtained from 4
30 patients, and demonstrates that the compound
31 inhibits this tumor cell proliferation in a
32 concentration dependent manner.

33 It will be understood by those skilled in the
34 art, that the ability of the RAR_α selective compounds

1 to significantly inhibit growth of malignant cells
2 in the above described assays is an indication that
3 these compounds can be administered with beneficial
4 effect to tumor bearing mammals (including humans)
5 for the treatment of tumors, particularly acute
6 monocytic leukemia, cervical carcinoma, myeloma,
7 ovarian carcinomas and head and neck carcinomas.

8 It has also been discovered in accordance with
9 the present invention that the proliferation of
10 retinal pigment epithelium cells is inhibited by RAR_α
11 selective compounds. By way of background it is
12 noted that after retinal detachment the retinal
13 pigment epithelium (RPE) becomes dedifferentiated,
14 proliferates and migrates into the subretinal space
15 (Campochiaro et al., Invest. Ophthal & Vis. Sci.
16 32:65-72 (1991)). Such processes therefore have an
17 impact upon the success of retinal reattachment
18 procedures. RAR agonists such as all-trans-retinoic
19 acid (ATRA) exhibit an antiproliferative effect upon
20 the growth rate of primary human RPE cultures
21 (Campochiaro et al., *ibid*) and have been shown to
22 decrease the incidence of retinal detachment after
23 retinal reattachment surgery in human studies
24 (Fekrat et al., Ophthalmology 102:412-418 (1994)).

25 The graph of Figure 5 shows the concentration
26 dependent inhibitory effect of all trans retinoic
27 acid (ATRA) and of Compound 42 on RPE proliferation
28 in an assay procedure which is described below.

29 Analysis of primary RPE cultures

30 Primary cultures of human retinal pigment
31 epithelium (RPE) were established from eyes as
32 previously described, (Campochiaro et al., Invest.
33 Ophthal & Vis. Sci. 32:65-72 (1991)). 5 X 10⁴ Cells
34 were plated in 16-mm wells of 24-well multiwell

1 plates in Dulbcco's modified Eagle's medium (DMEM
2 Gibco) containing 10% fetal bovine serum (FBS).
3 Cells were treated with ethanol alone (control),
4 ATRA (10^{-10} to 10^{-6} M) in ethanol, and Compound 42
5 (10^{-10} to 10^{-6} M) in ethanol. Cells were fed with
6 fresh media containing the appropriate
7 concentrations of these compounds every two days for
8 a total of six days treatment. Cells were removed
9 from the plates via treatment with trypsin and the
10 number of cells were counted with an electronic cell
11 counter. As it can be seen in Figure 5 treatment of
12 primary RPE cells with ATRA and with Compound 42
13 both led to a dose dependent decrease in RPE cell
14 proliferation.

15 The effect of topically administering to
16 experimental hairless mice RAR_{α} selective retinoid
17 compounds in accordance with the present invention
18 was also evaluated in a topical skin irritation
19 assay, using the RAR_{α} selective Compound 18 of the
20 invention. More particularly, skin irritation was
21 measured on a semi-quantitative scale by the daily
22 subjective evaluation of skin flaking and abrasions.
23 A single number, the topical irritation score,
24 summarizes the skin irritation induced in an animal
25 during the course of an experiment. The topical
26 irritation score is calculated as follows. The
27 topical irritation score is the algebraic sum of a
28 composite flaking score and a composite abrasion
29 score. The composite scores range from 0-9 and 0-8
30 for flaking and abrasions, respectively, and take
31 into account the maximum severity, the time of
32 onset, and the average severity of the flaking and
33 abrasions observed.

34 The severity of flaking is scored on a 5-point

1 scale and the severity of abrasions is scored on a
2 4-point scale, with higher scores reflecting greater
3 severity. The maximum severity component of the
4 composite scores would be the highest daily severity
5 score assigned to a given animal during the course
6 of observation.

7 For the time of onset component of the composite
8 score, a score ranging from 0 to 4 is assigned as
9 follows:

10

11 Time to Appearance of
12 Flaking or Abrasions of
13 Severity 2 or greater

14

(days)

Time of Onset Score

15

16

8

0

17

6-7

1

18

5

2

19

3-4

3

20

1-2

4

21

22 The average severity component of the composite
23 score is the sum of the daily flaking or abrasion
24 scores divided by the number of observation days.
25 The first day of treatment is not counted, since the
26 drug compound has not had an opportunity to take
27 effect at the time of first treatment.

28 To calculate the composite flaking and abrasion
29 scores, the average severity and time of onset
30 scores are summed and divided by 2. The result is
31 added to the maximal severity score. The composite
32 flaking and abrasion scores are then summed to give
33 the overall topical irritation score. Each animal
34 receives a topical irritation score, and the values

are expressed as the mean \pm SD of the individual scores of a group of animals. Values are rounded to the nearest integer.

Thus, female hairless mice [Cr1:SKH1-hrBR] (8-12 weeks old, n=4) were treated topically for 5 consecutive days with Compound 18 in doses expressed in nanomol/25 g, which is particularly given in Table 4. Treatments are applied to the dorsal skin in a total volume of 4 ml/kg (-0.1 ml). Mice were observed daily and scored for flaking and abrasions up to and including 3 days after the last treatment, i.e., day 8.

Table 4

Eight Day Topical Assay in Hairless Mice
of Compound 18

Dose	Mortality	Body Weight	Flaking	Abrasion	
Composite					
(out of 4)	% gain or	Score	Score	Score	
	(loss)				
100	0	8 \pm 7	0	1	1 \pm 1
1000	0	4 \pm 1	1	1	2 \pm 0
of TTNPB					
0.9	0	5 \pm 2	5	3	8 \pm 2
2.7	0	(4 \pm 3)	6	3	9 \pm 2
9	0	(11 \pm 3)	7	5	11 \pm 2

These data show that the RAR_α selective compound causes virtually no skin irritation and no weight

1 loss up to 1000 nmol/25g in the t st model. For
2 comparison it should be noted that the well known
3 prior art retinoid compound
4 4-(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnapht
5 halen-2-yl)propen-1-yl)benzoic acid (TTNPB), which
6 is not RAR_α selective, causes much more serious skin
7 irritation in the above-noted test, as is shown in
8 the foregoing table.

9 Another important advantage of administering
10 RAR_α selective retinoid compounds to a mammal lies in
11 the significantly reduced teratogenic potency of the
12 RAR_α selective compounds compared to many other
13 retinoids, as measured by a chondrogenesis
14 suppression bioassay. This assay is performed as
15 follows:

16 High-density "spot" cultures of limb bud
17 mesenchymal cells are used to compare the ability of
18 various concentrations of test drugs to suppress
19 chondrogenic differentiation as a bioassay.
20 Forelimb buds of mouse embryos on day 12 of
21 gestation (54 ± 2 somites) are dissociated in a
22 trypsin-EDTA solution, and the resultant single-cell
23 suspension is plated as 20- μ l spots (200,000
24 cells/spot) on plastic culture dishes. Retinoid
25 concentrations ranging from 0.3 ng/ml to 3 μ g/ml (1
26 nM-10 μ M) are added to the culture medium (Eagle's
27 MEM + 10% fetal bovine serum, GIBCO) 24 hours after
28 initial plating. Control cultures receive only the
29 vehicle (ethanol, concentration $\leq 1\%$ by vol);
30 Retinoic acid is used as a positive control in
31 another set of cultures.

32 The cultures are terminated 96 hours after
33 plating, at which time the medium is r moved and the
34 cells are fixed for 1 hour in 10% formalin

1 containing 0.5% c tylopyridinium chloride. The
2 cultures are rinsed in acetic acid and stained for 1
3 hour in 0.5% Alcian blue solution at pH 1.0,
4 differentiated in 3% acetic acid, and then
5 dehydrated in ethanol and scored for chondrogenesis
6 under the microscope. An absence or reduction in
7 the number of cartilage nodules in stained cultures
8 as compared with control cultures is taken as a
9 measure of suppression of chondrogenesis. The
10 number of cartilage nodules stained in the whole
11 spot, mean number of nodules, and standard
12 deviations are calculated for four replicate
13 cultures per treatment. The median concentration
14 causing a 50% inhibition of chondrogenesis compared
15 with controls (IC_{50}) is calculated by logarithmic
16 curve fitting of the dose-response data. The IC_{50}
17 values are expressed in nanogram per milliliter
18 (ng/ml) units. An IC_{50} value of greater
19 concentration in this assay signifies lesser
20 teratogenicity. Table 5 indicates the results
21 obtained in this assay for Compounds 10, 18, and 42
22 in accordance with the present invention, as well as
23 for comparison with all trans retinoic acid (ATRA)
24 and 4-(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetra-
25 methylnaphtha-len-2-yl)propen-1-yl)benzoic acid
26 (TTNPB).

Table 5

Compound	IC_{50} (ng/ml)
10	250
18	220
42	65
ATRA	55
TTNPB	0.01

1 As it can be seen the compounds used in
2 accordance with the present invention are less
3 teratogenic than all trans retinoic acid and
4 significantly (of the 10^4 order of magnitude) less
5 teratogenic than the prior art TTNPB compound.

6 Weight loss or gain that experimental animals
7 experience upon administration of retinoid compounds
8 is another test of the drug's toxicity, with
9 significant weight loss at relatively low doses
10 indicating a significant toxic side effect of the
11 retinoid. In one experiment, groups of 5 rats were
12 treated with varying doses (administered in corn
13 oil) of a test retinoid for 3 days. The rats were
14 euthanized 24 hours after the last dose. The graph
15 of Figure 6 shows the average weight of each group
16 of rats treated with a daily dose of 10, 30, and 90
17 $\mu\text{mol/kg/day}$ of Compound 42, as well as the average
18 weight of a group of control rats which were not
19 given the retinoid. As it can be seen, the RAR $_{\alpha}$
20 selective Compound 42 caused virtually no weight
21 loss, as compared to the control, except in a very
22 high dose (90 $\mu\text{mol/kg/day}$). The graph of Figure 7
23 shows the weight of the rats on the fourth day (24
24 hours after last administration of retinoid) in a
25 similar test with varying doses of Compound 18, with
26 a zero dose indicating the control. As it can be
27 seen, this RAR $_{\alpha}$ selective retinoid caused virtually
28 no weight loss even in the high dose of 90
29 $\mu\text{mol/kg/day}$. It is noteworthy that in similar tests
30 TTNPB, which binds to all three RAR receptor
31 subtypes (see Table 3) causes very significant
32 weight loss. In this experiment involving the rats
33 treated with Compound 42, significant mucocutaneous
34 toxicity was not observed.

1 In another experiment three-week old male
2 Hartley guinea pigs were implanted intraperitoneally
3 with osmotic pumps containing 20 % DMSO/80
4 polyethylene glycol (vehicle) or Compound 42 at
5 concentrations of 4.4, 13.3 or 40 mg/ml in vehicle.
6 Based on the initial body weights and known pumping
7 rate, approximate doses of 0, 2, 6, and 18 mg/kg/day
8 doses of Compound 42 are estimated. Body weights
9 and clinical observations were recorded at least
10 every other day for 14 days post-implantation. The
11 guinea pigs were euthanized after 14 days, and the
12 pumps were examined for possible failure. The graph
13 of Figure 8 shows the weight of the animals involved
14 in this experiment over the course of 15 days. As
15 it can be seen from the graph, the lower and middle
16 doses of the RAR_α selective retinoid compound
17 (Compound 42) caused no, or only statistically
18 insignificant depression of weight gain, relative to
19 the control animals. Significant depression of
20 weight gain was observed only in the high dose
21 (18mg/kg/day) of Compound 42. Importantly, no signs
22 of mucocutaneous toxicity were observed at any dose
23 of Compound 42 in this experiment. The foregoing,
24 markedly reduced mucocutaneous toxicity observed
25 when animals are treated with RAR_α selective
26 compounds in accordance with the present invention,
27 is a significant advantage, because mucocutaneous
28 toxicity is the major and most irksome retinoid side
29 effect or toxicity in human patients.

30 Synthetic Methods for Preparing the Preferred
31 Examples of RAR_α Selective Compounds of the Invention

32 General structure of the compounds which are
33 preferably used in the methods of treatment of the
34 present invention are shown above in Formula 1 and

1 **Formula 2.** These compounds can be made by the
2 synthetic chemical pathways illustrated here. The
3 synthetic chemist will readily appreciate that the
4 conditions set out here are specific embodiments
5 which can be generalized to any and all of the
6 compounds represented by these formulas.

7 Generally speaking the process of preparing
8 compounds preferably used in the methods of the
9 invention in accordance with **Formula 1** involves the
10 formation of an amide by the reaction of a compound
11 of the general **Formula 6** with a compound of general
12 **Formula 7**, or by the reaction of a compound of
13 general **Formula 6a** with a compound of general
14 **Formula 7a**. Similarly, the process of preparing
15 compounds in accordance with **Formula 2** involves the
16 formation of an amide by the reaction of a compound
17 of the general **Formula 8** with a compound of general
18 **Formula 7**, or by the reaction of a compound of
19 general **Formula 8a** with a compound of general
20 **Formula 7a**.

21 A compound of **Formula 6** is an acid or an
22 "activated form" of a carboxylic acid attached to
23 the aromatic portion of a tetrahydronaphthalene, (X_1
24 = $[C(R_1)_2]_n$ and n is 1), dihydroindene ($[C(R_1)_2]_n$ where
25 n is 0) or chroman (X_1 is 0) nucleus. The carboxylic
26 acid, or its "activated form" is attached to the 2
27 or 3 position of the tetrahydronaphthalene, and to
28 the 6 or 7 position of the chroman moieties. In the
29 compounds preferably used in accordance with the
30 invention the attachment is to the 2 position of
31 tetrahydronaphthalene and to the 6 position of
32 chroman.

33 The term "activated form" of the carboxylic acid
34 should be understood in this regard as such

1 derivativ of the carboxylic acid which is capable
2 of forming an amide wh n reacted with a primary
3 amine of Formula 7. In case of the "reverse amides"
4 the activated form of a carboxylic acid is a
5 derivative (Formula 7a) that is capable of forming
6 an amide when reacted with a primary amine of
7 Formula 6a. This, generally speaking, means such
8 derivatives of a carboxylic acid which are normally
9 known and used in the art to form amide linkages
10 with an amine. Examples of suitable forms or
11 derivatives for this purpose are acid chlorides,
12 acid bromides, and esters of the carboxylic acid,
13 particularly active esters, where the alcohol moiety
14 of the ester forms a good leaving group. Presently
15 most preferred as reagents in accordance with
16 Formula 6 (or Formula 7a) are acid chlorides (X, is
17 Cl). The acid chlorides of Formula 6 (or of Formula
18 7a) can be prepared by traditional methods from the
19 corresponding esters (X, is for example ethyl) by
20 hydrolysis and treatment with thionyl chloride
21 (SO₂Cl). The acid chlorides of Formula 6 (or of
22 Formula 7a) can also be prepared by direct treatment
23 of the carboxylic acids with thionyl chloride, where
24 the carboxylic acid, rather than an ester thereof is
25 available commercially or by a known synthetic
26 procedure. The acid chlorides of Formula 6 (or of
27 Formula 7a) are typically reacted with the amine of
28 Formula 7 (or amine of Formula 6a) in an inert
29 solvent, such as methylene chloride, in the presence
30 of an acid acceptor, such as pyridine.

31 The carboxylic acids themselves in accordance
32 with Formula 6 (or Formula 7a) are also suitable for
33 amide formation when reacted with an amine, a
34 catalyst (4-dimethylaminopyridine) in the presence

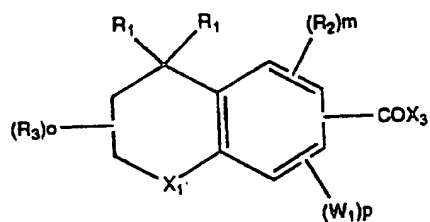
1 of a dehydrating agent, such as
2 dicyclohexylcarbodiimide (DCC) or more preferably
3 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
4 hydrochloride (EDC).

5 The carboxylic acids or the corresponding esters
6 of Formula 6, are generally speaking, prepared as
7 described in the chemical scientific or patent
8 literature and the literature procedures for their
9 preparation may be modified, if necessary, by such
10 chemical reactions or processes which per se are
11 known in the art. For example, generally speaking,
12 2,2, 4,4 and/or 2,2,4,4-substituted chroman
13 6-carboxylic acids and chroman 7-carboxylic acids
14 are available in accordance with the teachings of
15 United States Patent Nos. 5,006,550, 5,314,159,
16 5,324,744, and 5,348,975, the specifications of
17 which are expressly incorporated herein by
18 reference. 5,6,7,8-Tetrahydronaphthalene-2-
19 carboxylic acids are, generally speaking, available
20 in accordance with the teachings of United States
21 Patent No. 5,130,335, the specifications of which is
22 expressly incorporated herein by reference.

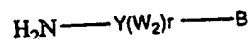
23 The foregoing general description of the
24 reactions which lead to formation of the amides of
25 Formula 1 is also, generally speaking, applicable to
26 the formation of the amides of Formula 2. The
27 reagents which are used in accordance with the
28 general principles mentioned above for the formation
29 of amide compounds of Formula 2 are: activated forms
30 of a carboxylic acids shown in Formula 8 and in
31 Formula 7a, and the amines of Formula 7 and of
32 Formula 8a.

33

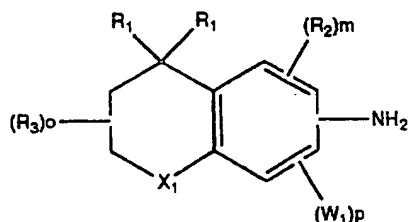
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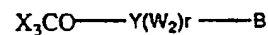
Formula 6



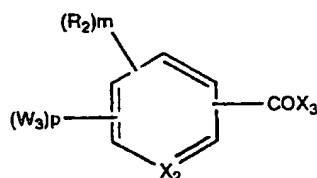
Formula 7



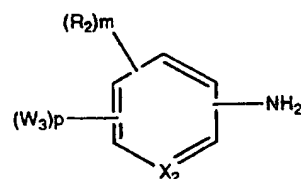
Formula 6a



Formula 7a



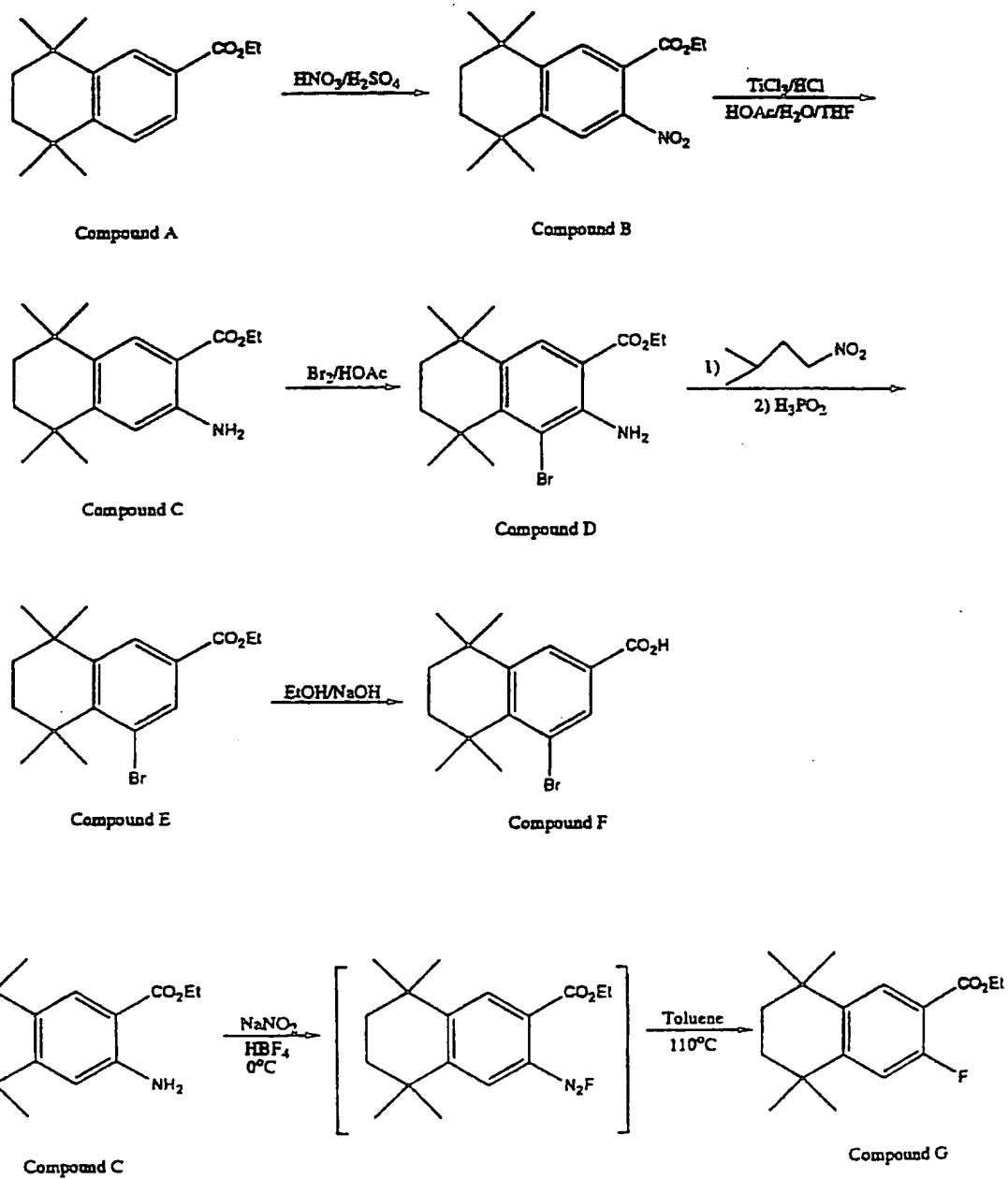
Formula 8



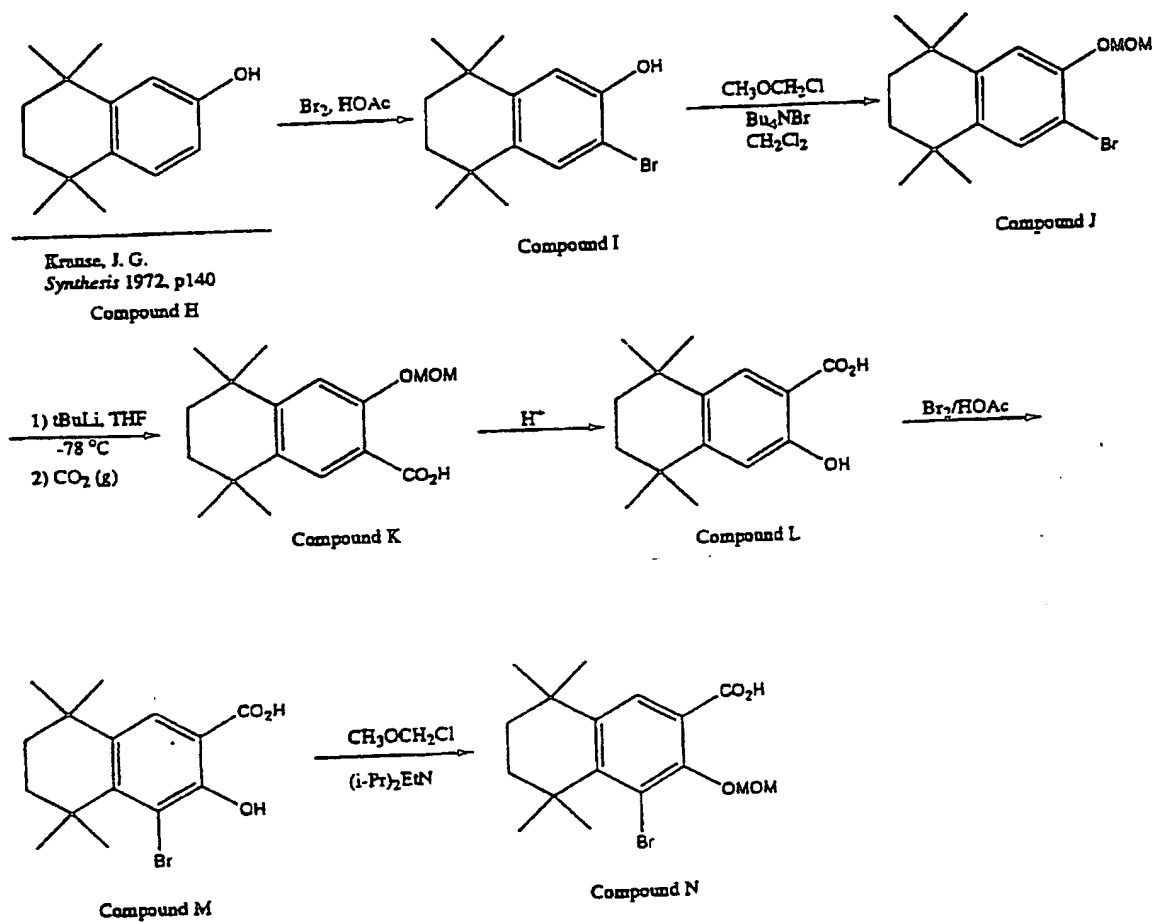
Formula 8a

The carboxylic acids or the corresponding esters of Formula 8, are generally speaking, prepared as described in the chemical scientific or patent literature and the literature procedures for their preparation may be modified, if necessary, by such chemical reactions or processes which per se are known in the art.

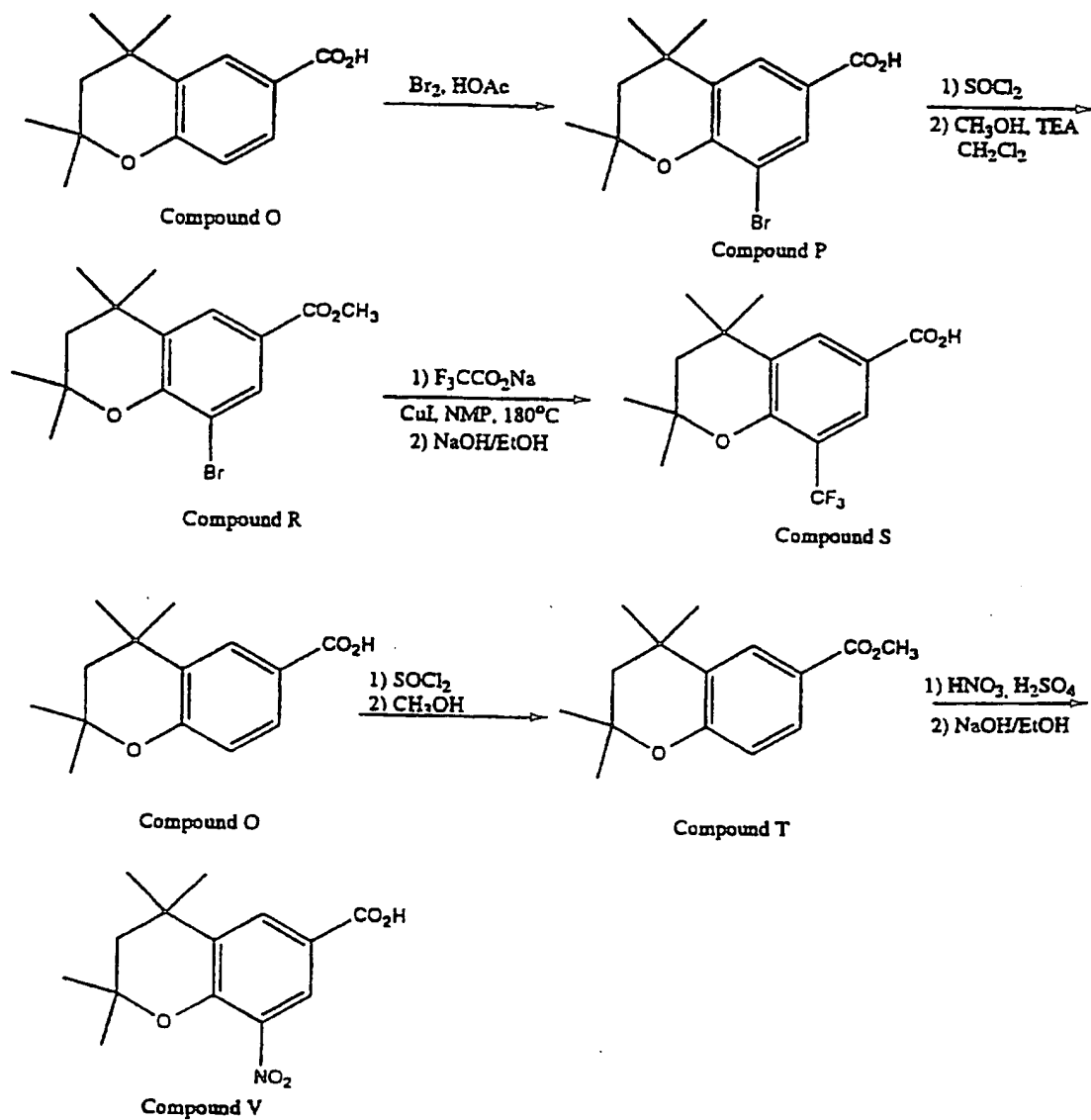
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Reaction Scheme 1



Reaction Scheme 2



Reaction Scheme 2 (continued)

1 Reaction Schemes 1 and 2 provide examples for
2 the synthesis of derivatives of 5,6,7,8-tetrahydro-
3 5,5,8,8-tetramethyl-naphthalene-2-carboxylic acid,
4 which are within the scope of Formula 6 and which
5 are reacted with an amine of Formula 7 to provide
6 (5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-
7 2-yl)carbamoyl derivatives within the scope of
8 Formula 1. Thus, as is shown in Reaction Scheme 1,
9 ethyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-
10 naphthalene-2-carboxylate (Compound A) is nitrated
11 to provide the corresponding 3-nitro compound
12 (Compound B). The nitro group of Compound B is
13 reduced to provide the corresponding 3-amino
14 compound (Compound C) which is described in the
15 publication Lehmann et al. Cancer Research, 1991,
16 51, 4804. Ethyl 5,6,7,8-tetrahydro-5,5,8,8-tetra-
17 methyl-3-amino-naphthalene-2-carboxylate (Compound
18 C) is brominated to yield the corresponding 4-bromo
19 derivative (Compound D), which is converted by
20 treatment with isoamylnitrite and reduction with
21 H_3PO_2 , to ethyl 5,6,7,8-tetrahydro-5,5,8,8-tetra-
22 methyl- 4-bromonaphthalene-2-carboxylate (Compound
23 E). Saponification of Compound E yields
24 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-4-bromonaphth
25 alene-2-carboxylic acid (Compound F) which is used
26 as a reagent in accordance with Formula 6. Ethyl
27 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-aminonaphth
28 alene-2-carboxylate (Compound C) is also diazotized
29 and reacted with HBF_4 to provide ethyl
30 5,6,7,8-tetrahydro-5,5,8,8-tetra-methyl-3-fluoronaph
31 thalene-2-carboxylate (Compound G) which serves
32 either per se or after saponification as a reagent
33 in accordance with Formula 6.

34 5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-

1 hydroxynaphthalene (Compound H, available in
2 accordance with the publication Krause Synthesis
3 1972 140), is the starting material in the example
4 shown in Reaction Scheme 2. Compound H is
5 brominated to provide the corresponding 3-bromo
6 compound (Compound I) which is thereafter protected
7 in the hydroxyl function by treatment with
8 methoxymethyl chloride (MOMCl) to yield
9 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methoxymet-
10 hoxy-2-bromonaphthalene (Compound J). Compound J is
11 reacted with t-butyllithium and carbon dioxide to
12 provide the corresponding carboxylic acid (Compound
13 K) from which the methoxymethyl protecting group is
14 removed by acid to give
15 5,6,7,8-tetrahydro-5,5,8,8-tetra-
16 methyl-2-hydroxynaphthalene-3-carboxylic acid
17 (Compound L). Compound L is brominated to yield
18 5,6,7,8-tetrahy-
19 dro-5,5,8,8-tetramethyl-1-bromo-2-hydroxynaphthalene
20 -3-carboxylic acid (Compound M). Compound L and
21 Compound M serve as reagents in accordance with
22 Formula 6. The hydroxy group of Compound M is
23 protected for further transformations with
24 methoxymethyl chloride (MOMCl) in the presence of
25 base, yielding 5,6,7,8-tetrahydro-5,5,8,8-
26 tetramethyl-1-bromo-2-methoxymethoxynaphthalene-3-ca
27 rboxylic acid (Compound N).

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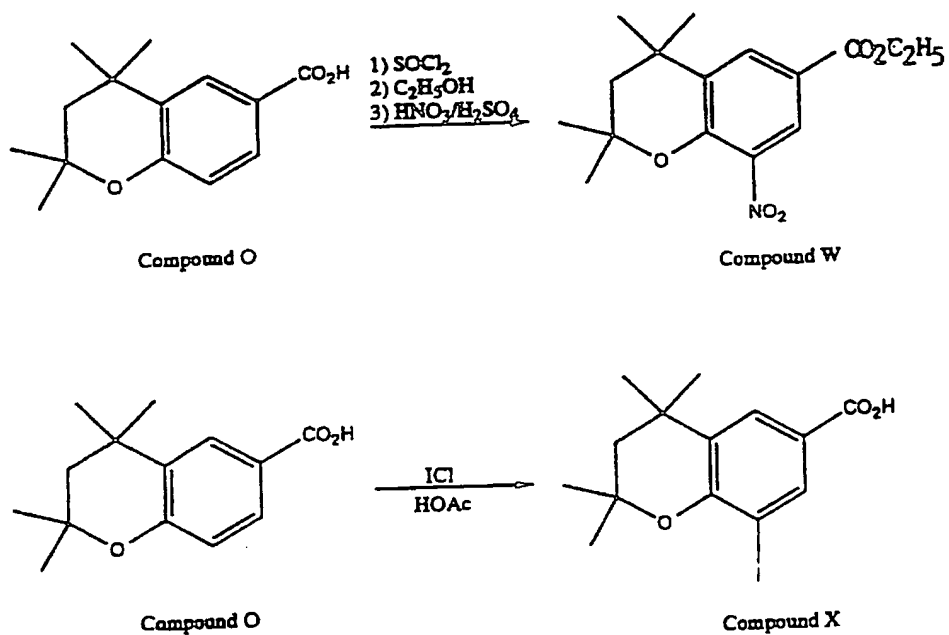
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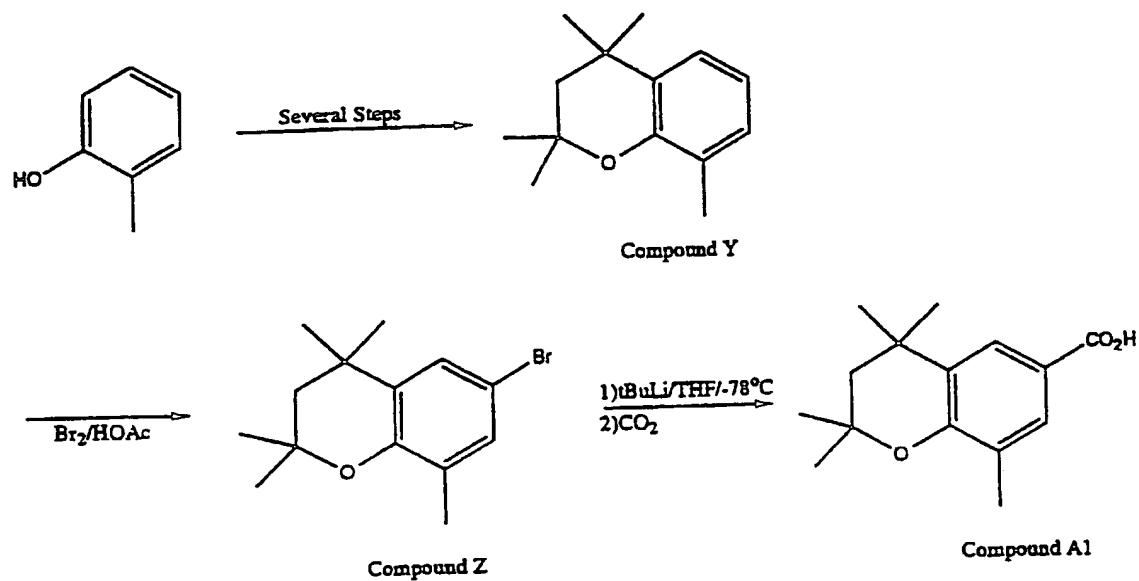
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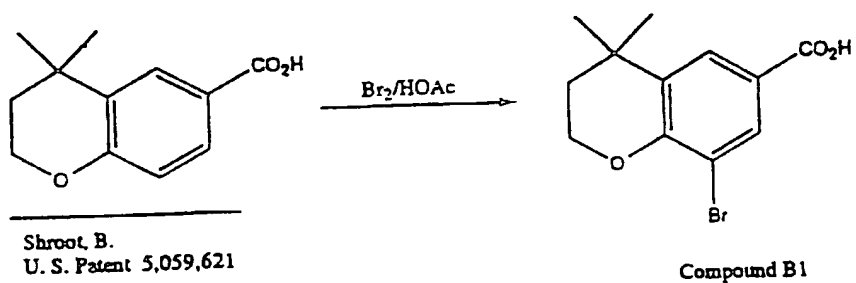
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Reaction Scheme 3



Reaction Scheme 4



Reaction Scheme 5

1 Reaction Schemes 3, 4 and 5 provide examples for
2 the synthesis of derivativ s of 2,2,4,4 and
3 4,4-substituted chroman-6-carboxylic acids which can
4 serve as reagents in accordance with Formula 6 for
5 the synthesis of the carbamoyl (amide) compounds
6 within the scope of the present invention. Thus,
7 referring now to Reaction Scheme 3,
8 2,2,4,4-tetramethylchroman-6-carboxylic acid
9 (Compound O, see U. S. Patent No. 5,006,550) is
10 brominated with bromine in acetic acid to yield the
11 corresponding 8-bromo derivative (Compound P).
12 Compound P is converted to the acid chloride by
13 treatment with thionyl chloride, and the resulting
14 acid chloride is suitable for reaction with an amine
15 of Formula 3 to provide the carbamoyl (amide)
16 compounds of the invention. The acid chloride is
17 also reacted with an alcohol (methanol) in the
18 presence of base to yield the corresponding ester,
19 methyl 2,2,4,4-tetramethyl-8-bromochroman-6-
20 carboxylate (Compound R). The bromo function of
21 Compound R is converted to a trifluoromethyl
22 function by treatment with sodium trifluoroacetate
23 in the presence of cuprous iodide catalyst and
24 1-methyl-2-pyrrolidinone (NMP), and the carboxylate
25 ester group is saponified to yield
26 2,2,4,4-tetramethyl-8-trifluoromethylchroman-6-carbo-
27 xylic acid (Compound S). Compound S is within the
28 scope of Formula 6 and is suitable per se or as the
29 acid chloride or in other "activated" form to react
30 with the amines of Formula 7 to yield the carbamoyl
31 (amide) compounds of the invention.
32 2,2,4,4-Tetramethylchroman-6-carboxylic acid
33 (Compound O) is also convert d to the methyl ester
34 (Compound T) which is then nitrated to yield

1 2,2,4,4-tetramethyl-8-nitrochroman-6-carboxylic acid
2 (Compound V), still another reagent within the scope
3 of Formula 6. Moreover, in the example further
4 shown in Reaction Scheme 3,
5 2,2,4,4-tetramethylchroman-6-carboxylic acid
6 (Compound O) is converted to the ethyl ester and
7 nitrated thereafter to yield ethyl
8 2,2,4,4-tetramethyl-8-nitrochroman-6-carboxylate
9 (Compound W). Still further, Compound O is reacted
10 with ICl to yield 2,2,4,4-tetramethyl-8-iodochroman-
11 6-carboxylic acid (Compound X).

12 In accordance with the example shown in Reaction
13 Scheme 4, 2-methylphenol is subjected to a series of
14 reactions in accordance with the teachings of United
15 States Patent No. 5,045,551 (incorporated herein by
16 reference) to yield 2,2,4,4,8-pentamethylchroman
17 (Compound Y). Compound Y is brominated with bromine
18 in acetic acid to give 2,2,4,4,8-pentamethyl-6-
19 bromochroman (Compound Z) which is reacted with
20 t-butyl lithium and thereafter with carbon dioxide
21 to give 2,2,4,4,8-pentamethylchroman-6-carboxylic
22 acid (Compound A₁).

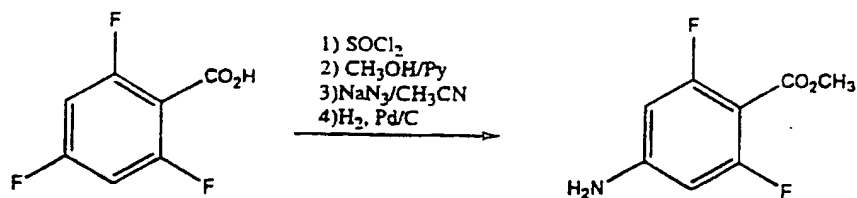
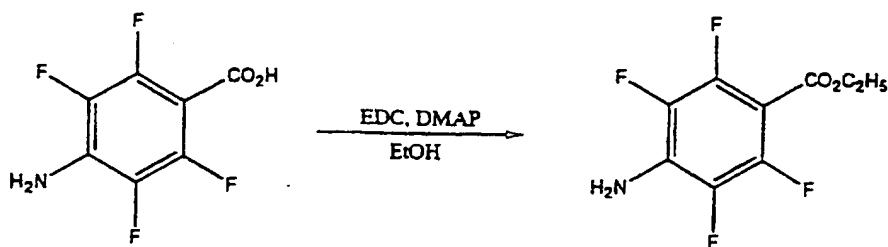
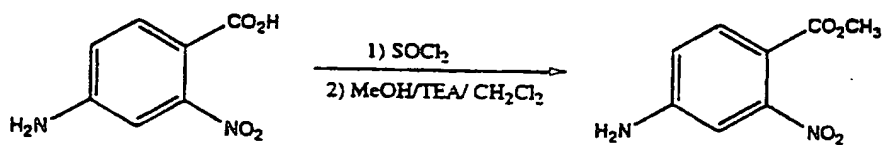
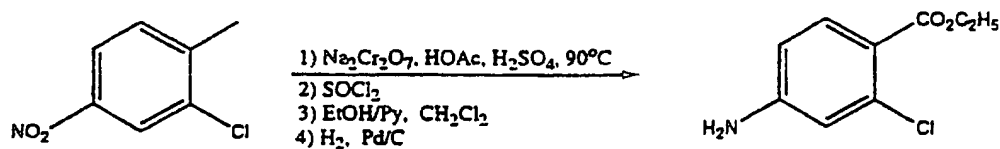
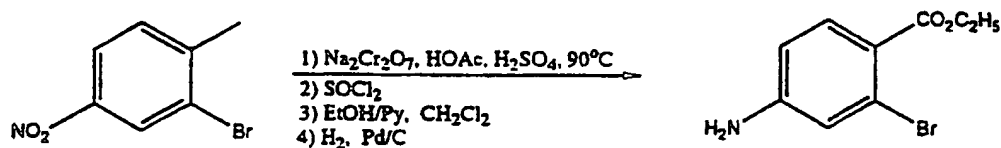
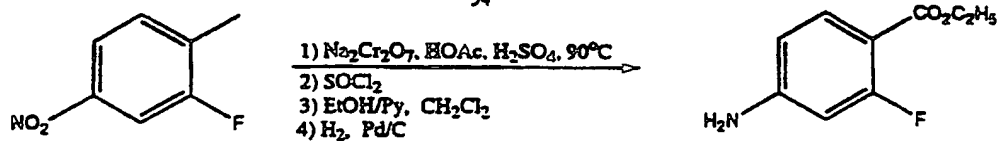
23 Reaction Scheme 5 illustrates the synthesis of
24 4,4-dimethyl-8-bromochroman-6-carboxylic acid
25 (Compound B₁) by bromination of
26 4,4,-dimethyl-chroman-6-carboxylic acid which is
27 available in accordance with the teachings of United
28 States Patent No. 5,059,621, the specification of
29 which is incorporated herein by reference.
30 2,2,4,4,8-Pentamethylchroman-6-carboxylic acid
31 (Compound A₁) and 4,4,-dimethyl-8-bromochroman-
32 6-carboxylic acid (Compound B₁) serve as reagents,
33 either per se, or as the corresponding acid
34 chlorides (or other "activated form), in accordance

1 with Formula 6 for the synthesis of the carbamoyl
2 (amide) compounds of the present invention.

3 Referring back now to the reaction between the
4 reagent of Formula 6 with an amine compound of
5 Formula 7 it is noted that the amine compounds are,
6 generally speaking, available in accordance with the
7 state-of-the-art. as described in the scientific and
8 patent literature. More specifically, the amine
9 compounds of Formula 7 can be prepared as described
10 in the scientific and patent literature, or from
11 known compounds of the literature, by such chemical
12 reactions or transformations which are within the
13 skill of the practicing organic chemist. Reaction
14 Scheme 6 illustrates examples for the preparation of
15 amine compounds of Formula 7 (where Y is phenyl)
16 from commercially available starting materials
17 (Aldrich Chemical Company, or Research Plus, Inc.).
18 The illustrated compounds of Formula 7 are used for
19 the synthesis of several preferred compounds used in
20 the methods of the invention.

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Reaction Scheme 6

1 Thus, in accordance with Reaction Scheme 6,
2 3-nitro-6-methyl-fluorobenzene (Aldrich) is
3 subjected to oxidation, conversion of the resulting
4 carboxylic acid to an acid chloride and thereafter
5 to an ethyl ester, followed by reduction of the
6 nitro group, to yield ethyl
7 2-fluoro-4-amino-benzoate (Compound C₁).
8 3-Nitro-6-methyl-bromobenzene (Aldrich) and
9 3-nitro-6-methyl-chlorobenzene (Aldrich) are
10 subjected to essentially to the same series of
11 reactions to yield ethyl 2-bromo-4-amino-benzoate
12 (Compound D₁) and ethyl 2-chloro-4-amino-benzoate
13 (Compound E₁), respectively. 2-Nitro-4-aminobenzoic
14 acid (Research Plus) is converted to its methyl
15 ester (Compound F₁) through the corresponding acid
16 chloride. 2,3,5,6-Tetrafluoro-4-amino-benzoic acid
17 (Aldrich) is esterified by treatment with ethanol in
18 the presence of 1-(3-dimethylaminopropyl)-3-
19 ethylcarbodiimide hydrochloride (EDC) and
20 4-dimethylaminopyridine in CH₂Cl₂ to give ethyl
21 2,3,5,6-tetrafluoro-4-amino-benzoate (Compound G₁).
22 2,4,6-Trifluorobenzoic acid (Aldrich) is converted
23 to the methyl ester through the acid chloride, and
24 the 4-fluoro atom is displaced by reaction with
25 sodium azide, followed by hydrogenation, to yield
26 methyl 2,6-difluoro-4-amino benzoate (Compound H₁).
27 Compounds C₁, D₁, E₁, F₁, G₁ and H₁ serve as amine
28 reagents in accordance with Formula 7. Further
29 examples of reagents in accordance with Formula 7
30 are nitro, fluoro, chloro, bromo and trifluoromethyl
31 derivatives of amino substituted heteroaryl
32 carboxylic acids, or their lower alkyl esters, such
33 as ethyl 2-amino-4-chloropyridine 2-carboxylate,
34 ethyl 5-amino-3-chloropyridine 5-carboxylate, and

1 3,4-dibromo-5-aminothiophene-2-carboxylic acid. Th
2 latter examples qcan be prepared by respective
3 chlorination or bromination of
4 2-aminopyridine-5-carboxylic acid or of its ester,
5 3-aminopyridine-6-carboxylic acid or of its ester
6 (described in WO 93/06086) and of
7 2-aminothiophene-5-carboxylic acid (described in
8 PCT/US92/06485).

9 The reactions between the compounds of Formula 6
10 and Formula 7 or between compounds of Formula 6a and
11 7a, described above, comprise the actual syntheses
12 of the carbamoyl (amide) compounds of the invention.
13 Numerous examples of this reaction are described in
14 detail in the experimental section below. The
15 carbamoyl (amide) compounds of the invention can be
16 converted into thiocarbamoyl (thioamide) compounds
17 of the invention where with reference to Formula 1 Z
18 is S, by reacting the carbamoyl (amide) compound
19 with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-
20 diphosphetane-2,4-disulfide (Lawesson's reagent).
21 This reaction is illustrated in Reaction Scheme 7
22 for two specific examples for the compounds used in
23 the methods of the invention.

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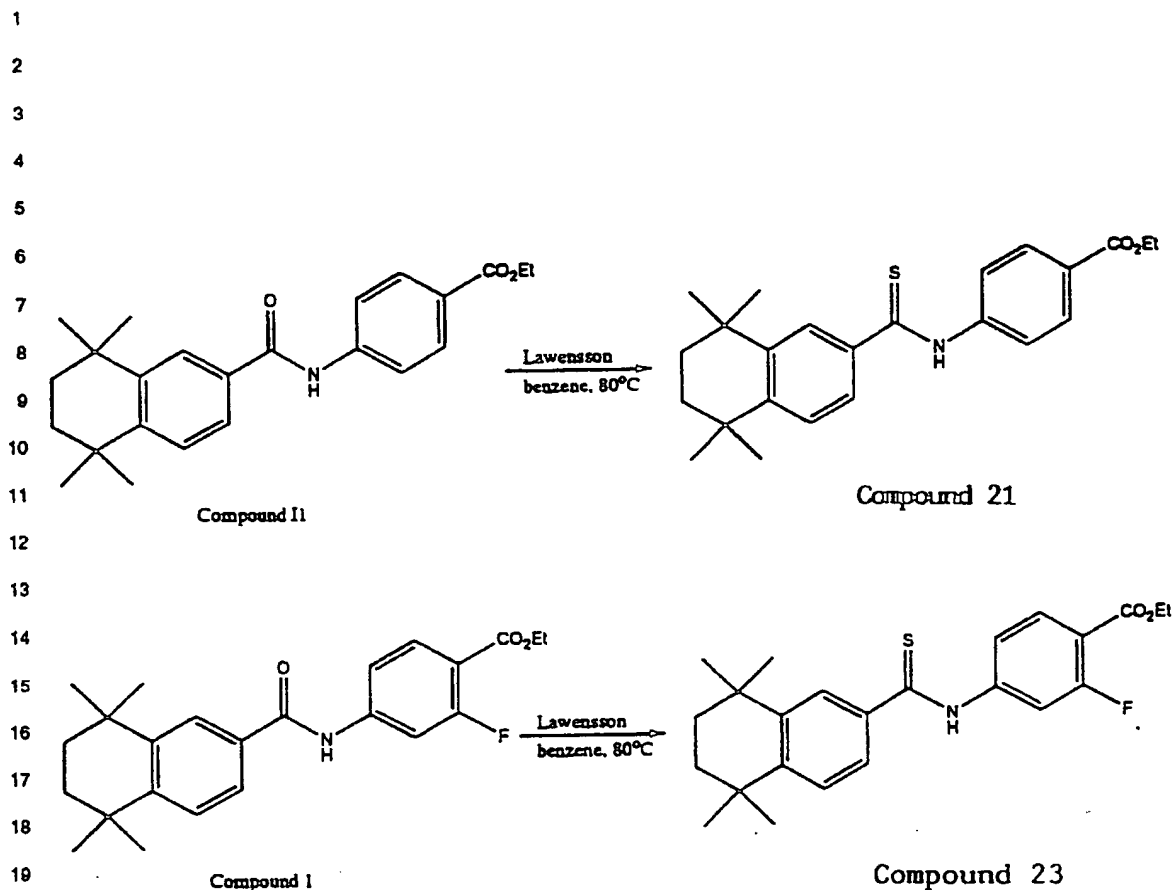
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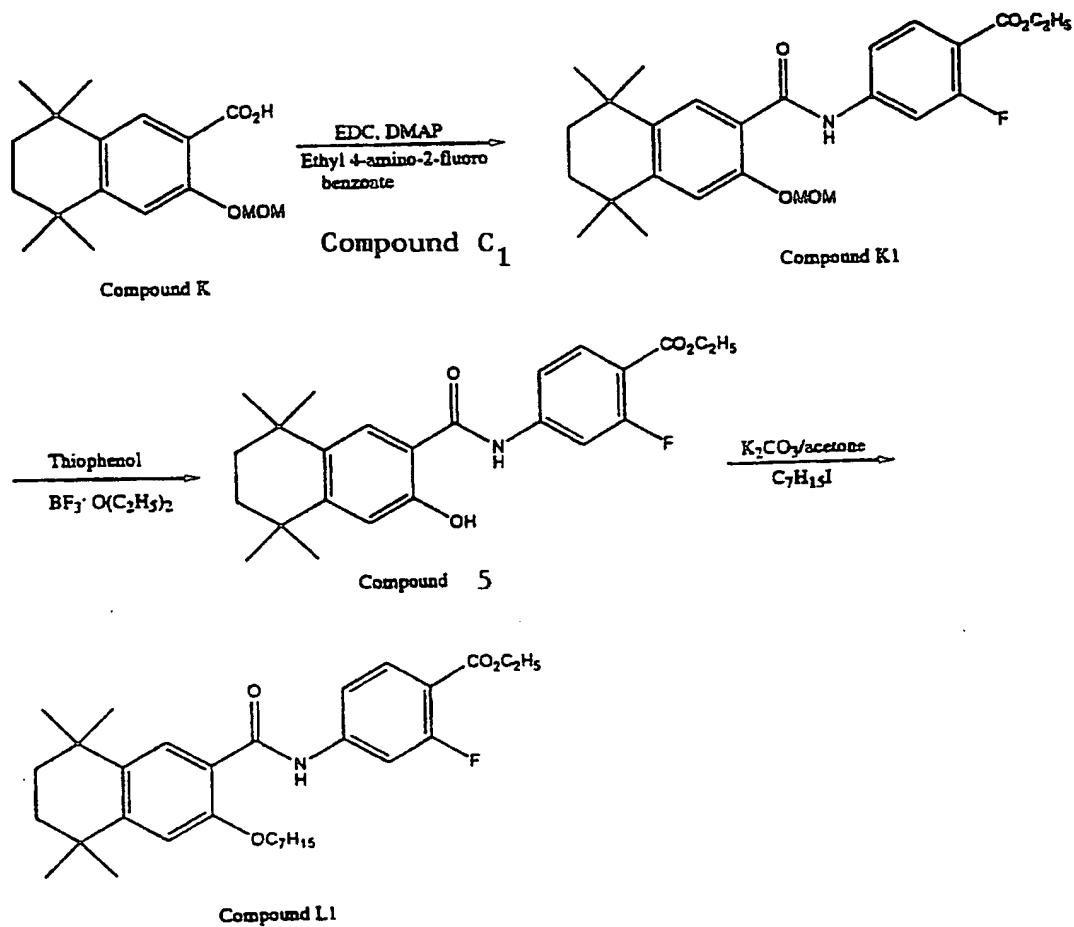
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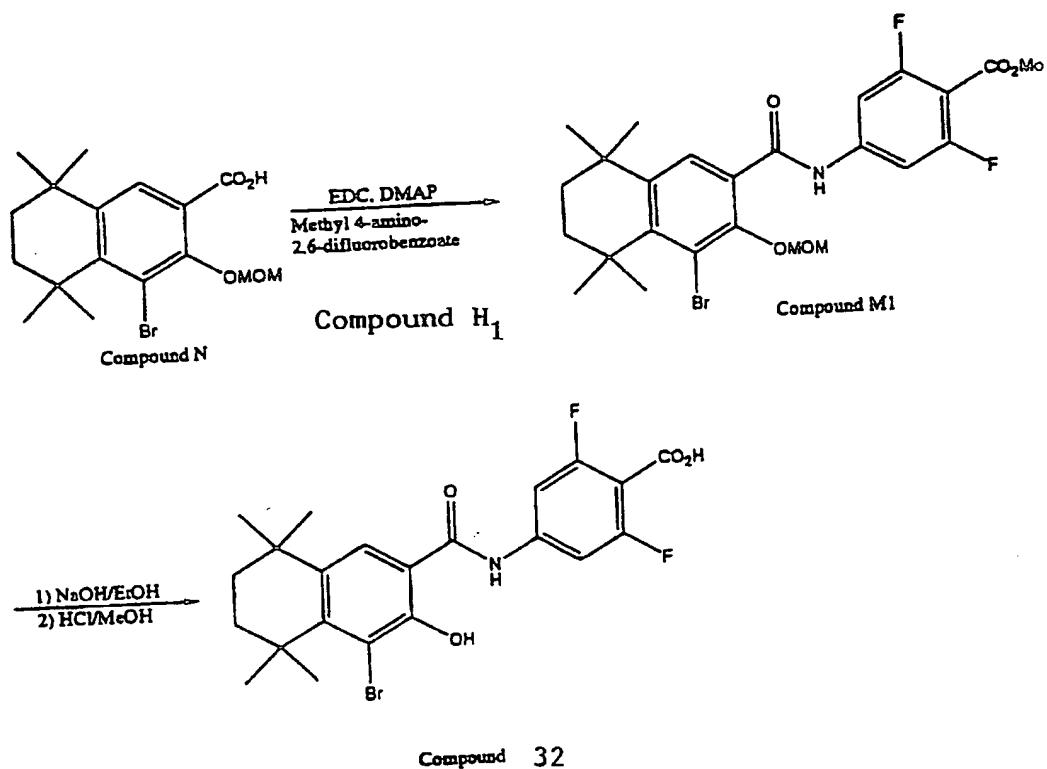
Reaction Scheme 7

25 In Reaction Scheme 7 one starting material ethyl
26 4-[5',6',7',8'-tetrahydro-5',5',8',8'-tetramethyl-
27 naphthalen-2-yl)carbamoyl]benzoate (Compound I₁) is
28 obtained in accordance with the teachings of
29 Kagechika et al. J. Med Chem. 1988 31, 2182 - 2192.
30 The other starting material, ethyl
31 2-fluoro-4-[5',6',7',8'-tetrahydro-5',5',8',8'-tetra
32 methylnaphthalen-2-yl)carbamoyl]benzoate (Compound
33 1) is obtained in accordance with the present
34 invention.

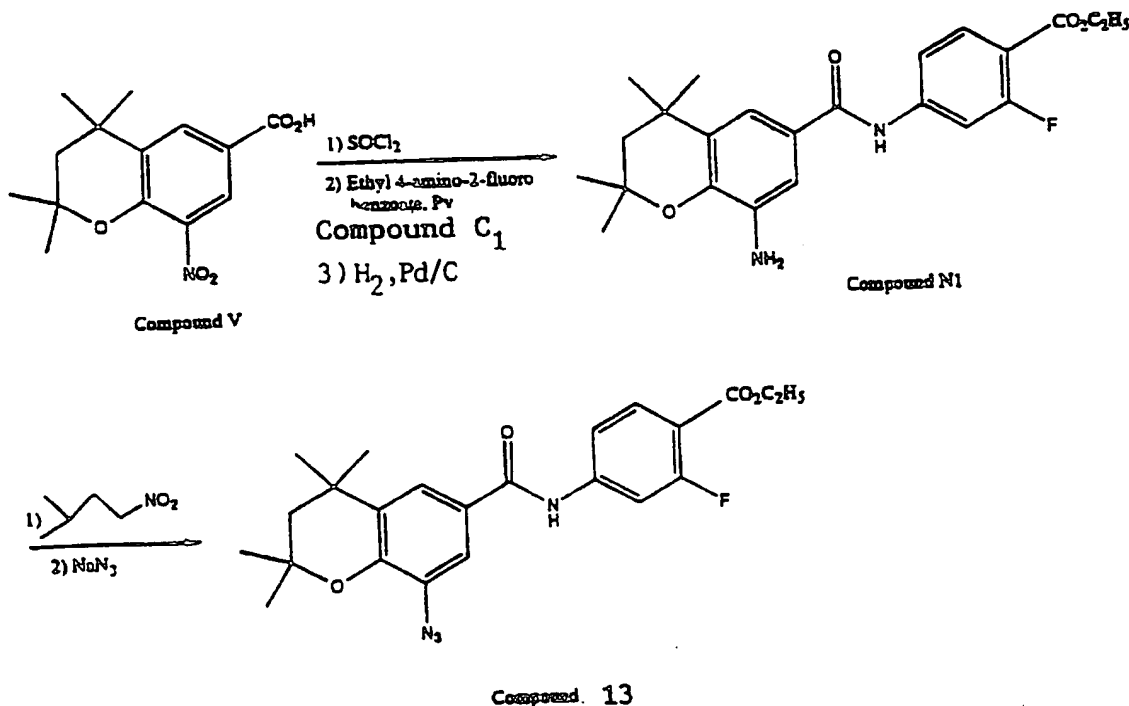


Reaction Scheme 8

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Reaction Scheme 9



Reaction Scheme 10

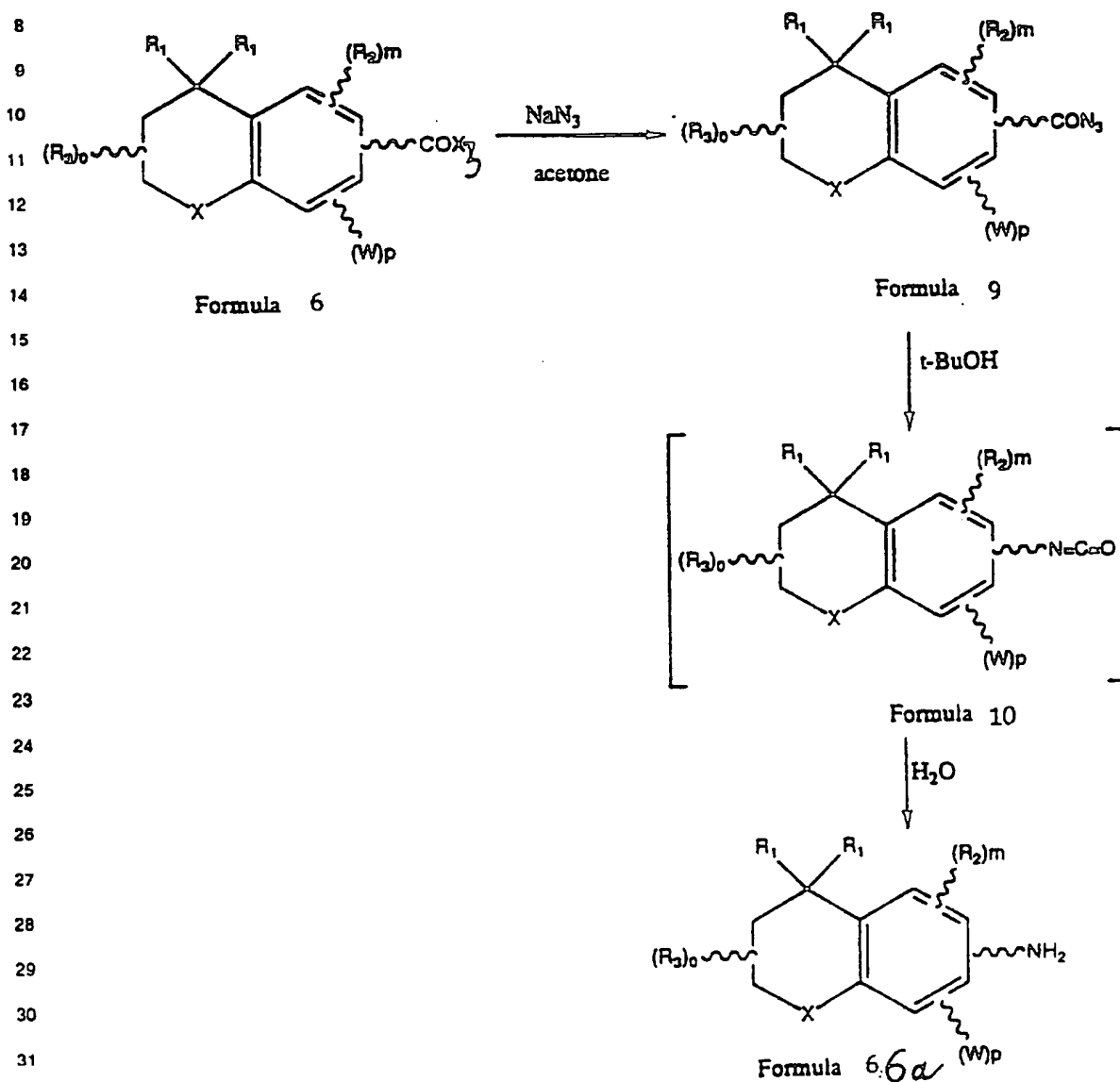
20 Reaction Schemes 8, 9 and 10 disclose examples
21 for the preparation of carbamoyl (amide) compounds
22 of the invention, first by a coupling reaction of a
23 compound of Formula 6 with a compound of Formula 7,
24 followed by one or more reactions performed on the
25 carbamoyl (amide) compound that has been first
26 obtained directly in the coupling reaction. Thus,
27 as is shown in Reaction Scheme 8,
28 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-
29 3-methoxymethoxynaphthalene-2-carboxylic acid
30 (Compound K) is coupled with ethyl
31 4-amino-2-fluorobenzoate (Compound C_1) in CH_2Cl_2 in
32 the presence of 1-(3-dimethylaminopropyl)-3-
33 ethylcarbodiimide hydrochloride (EDC) and
34 dimethylaminopyridine (DMAP) to give ethyl

1 2-fluoro-4-[5',6',7',8'-tetrahydro-5',5',8',8'-tetra
2 methyl-2'-methoxymethoxy-naphthalen-
3 3'-yl)carbamoyl]benzoate (Compound K₁). The
4 methoxymethyl protecting group is removed from
5 Compound K₁ by treatment with thiophenol and
6 borontrifluoride etherate resulting in ethyl
7 2-fluoro-4-[5',6',7',8'-tetrahydro-5',5',8',8'-tetra
8 methyl-2'-hydroxy-naphthalen-3'-yl)carbamoyl]-
9 benzoate (Compound 5). The hydroxy function of
10 Compound 5 is converted into an n-hexyl ether by
11 treatment with hexyl iodide in the presence of mild
12 base.

13 In accordance with Reaction Scheme 9
14 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-1-bromo-2-met
15 hoxymethoxynaphthalene-3-carboxylic acid (Compound
16 N) is coupled with methyl 4-amino-2,6-difluoro-
17 benzoate (Compound H₁) in CH₂Cl₂ solvent in the
18 presence of ethylcarbodiimide hydrochloride (EDC)
19 and DMAP to provide methyl
20 2,6-difluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-
21 tetramethyl-1'-bromo-2'-methoxymethoxy-naphthalen-3'
22 -yl)carbamoyl]benzoate (Compound M₁), from which the
23 esterifying methyl group and the methoxymethyl
24 protecting group are removed by treatment with base
25 and acid, respectively to yield
26 2,6-difluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-
27 tetramethyl-1'-bromo-2'-hydroxy-naphthalen-3'-yl)car
28 bamoyl]benzoic acid (Compound 32).

29 Reaction Scheme 10 discloses the example of
30 converting 2,2,4,4-tetramethyl-8-nitrochroman-6-
31 carboxylic acid (Compound V) into the corresponding
32 acid chloride by treatment with thionyl chloride,
33 followed by coupling with ethyl
34 4-amino-2-fluorobenzoate (Compound C₁) and

hydrogenation to yield ethyl
 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-amino-6'-chromanyl)carbamoyl]benzoate (Compound N₁). Compound N₁ is converted to the corresponding 8-azido compound, ethyl 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-azido-6'-chromanyl)carbamoyl]benzoate (Compound 13) by treatment with isoamyl nitrate and NaN₃.



Reaction Scheme 11

1 Reaction Scheme 11 illustrates the synthesis of
2 the primary amine compounds of Formula 6a from the
3 acid chlorides ($X_3 = Cl$) or other form of activated
4 acids of Formula 6 where the primary amine of
5 Formula 6a is not available by a published
6 literature procedure. Thus, substantially in
7 accordance with the step of a Curtius rearrangement,
8 the acid chloride of Formula 6 is reacted with
9 sodium azide in acetone to yield the azide compound
10 of Formula 9. The azide of Formula 9 is heated in a
11 polar high boiling solvent, such as *t*-butanol, to
12 provide the intermediate isocyanate of Formula 10,
13 which is hydrolyzed to yield a compound of Formula
14 6a.

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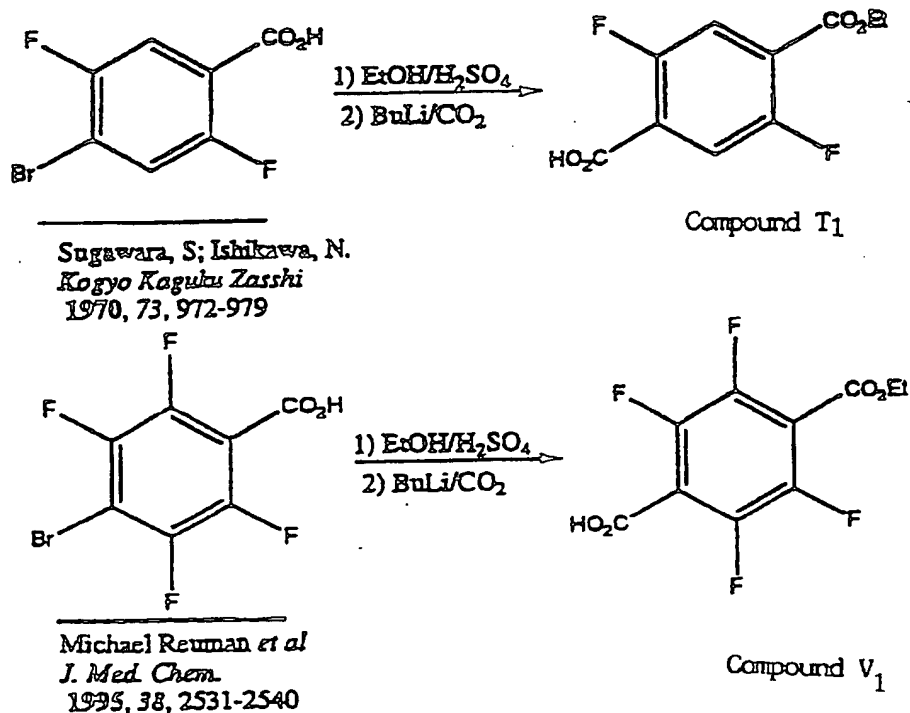
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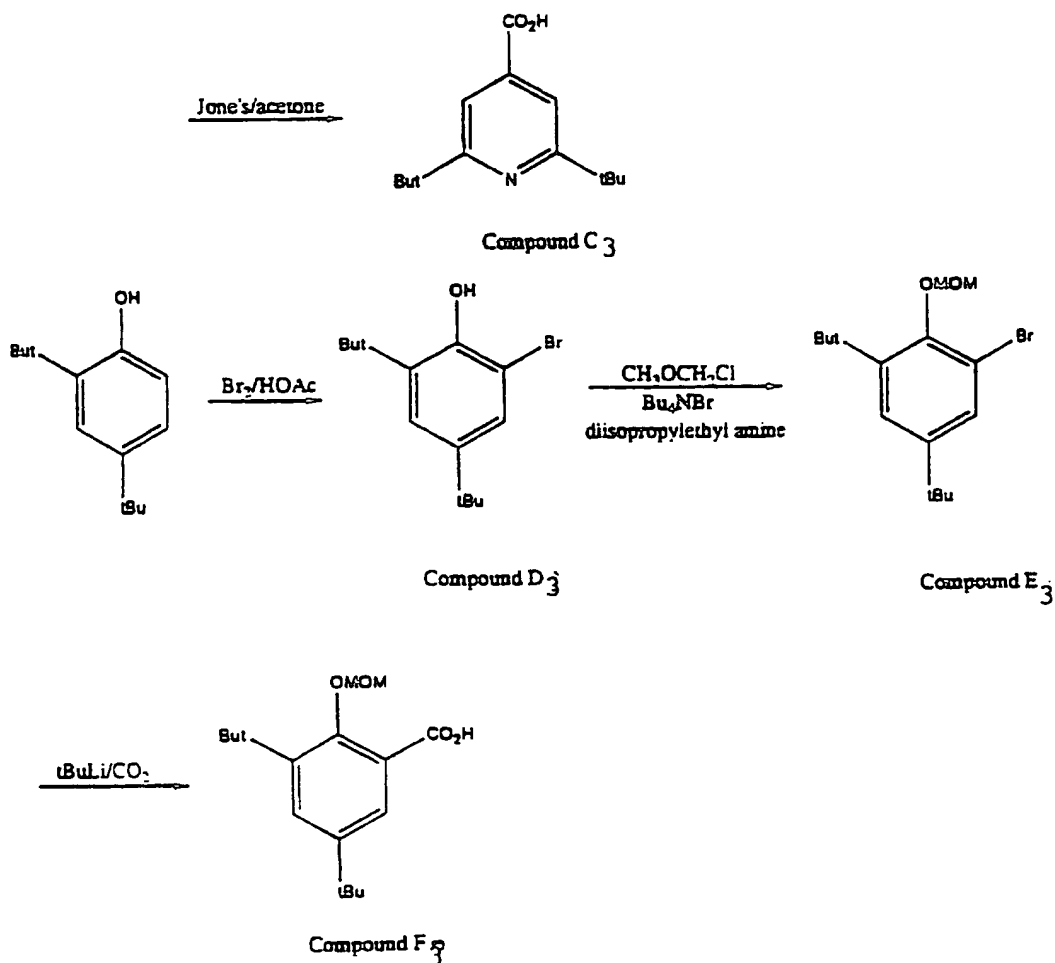
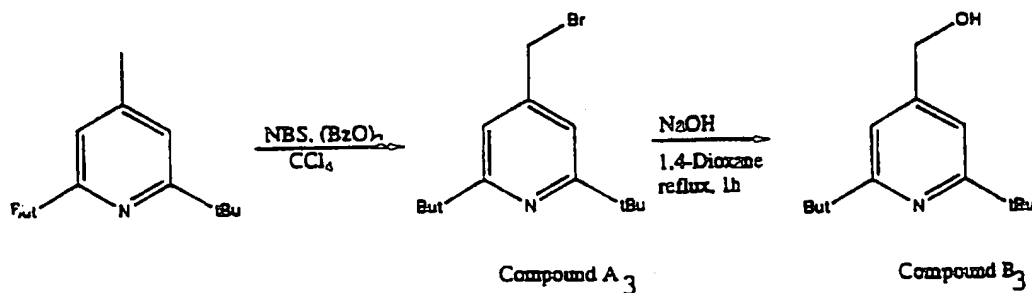


Reaction Scheme 12

1 Reaction Scheme 12 illustrates examples for
2 preparing compounds of Formula 7a where such
3 compounds are not available commercially or by a
4 published literature procedure. Thus, by way of
5 example 2,5-difluoro-4-bromobenzoic acid (available
6 by the literature procedure of Sugawara et al. Kogyo
7 Kagaku Zasshi 1970, 73, 972-979) is first esterified
8 by treatment with ethyl alcohol and acid to yield
9 the corresponding ester, and thereafter is reacted
10 with butyl lithium followed by carbon dioxide to
11 give the monoester of 2,5-difluoro terephthalic acid
12 (Compound T₁). A similar sequence of reactions
13 performed on 2,3,5,6-difluoro-4-bromobenzoic acid
14 (available by the literature procedure of Reuman et
15 al. J. Med. Chem. 1995, 38, 2531-2540) yields the
16 monoester of 2,3,5,6-tetrafluoroterephthalic acid
17 (Compound V₁). The just illustrated sequence of
18 reaction can be, generally speaking, utilized for
19 the synthesis of all compounds of Formula 7a with
20 such modification which will become readily apparent
21 to those skilled in the art, where such compounds
22 are not available by a known literature procedure.

23 Reaction Scheme 13 provides an example for the
24 preparation of 2,6-di-tert-butylisonicotinic acid
25 (Compound C₁) which is a reagent in accordance with
26 Formula 8 for the preparation of several preferred
27 compounds of the present invention. Thus,
28 2,6-di-tert-butyl-4-methylpyridine (available
29 commercially from Aldrich Chemical Co.) is reacted
30 with N-bromosuccinimide and benzoyl peroxide to
31 provide 4-bromomethyl-2,6-di-tert-butylpyridine
32 (Compound A₁). Compound A₁ is reacted with base
33 (sodium hydroxyde) to yield the coresponding
34 hydroxymethyl compound (Compound B₁), which is

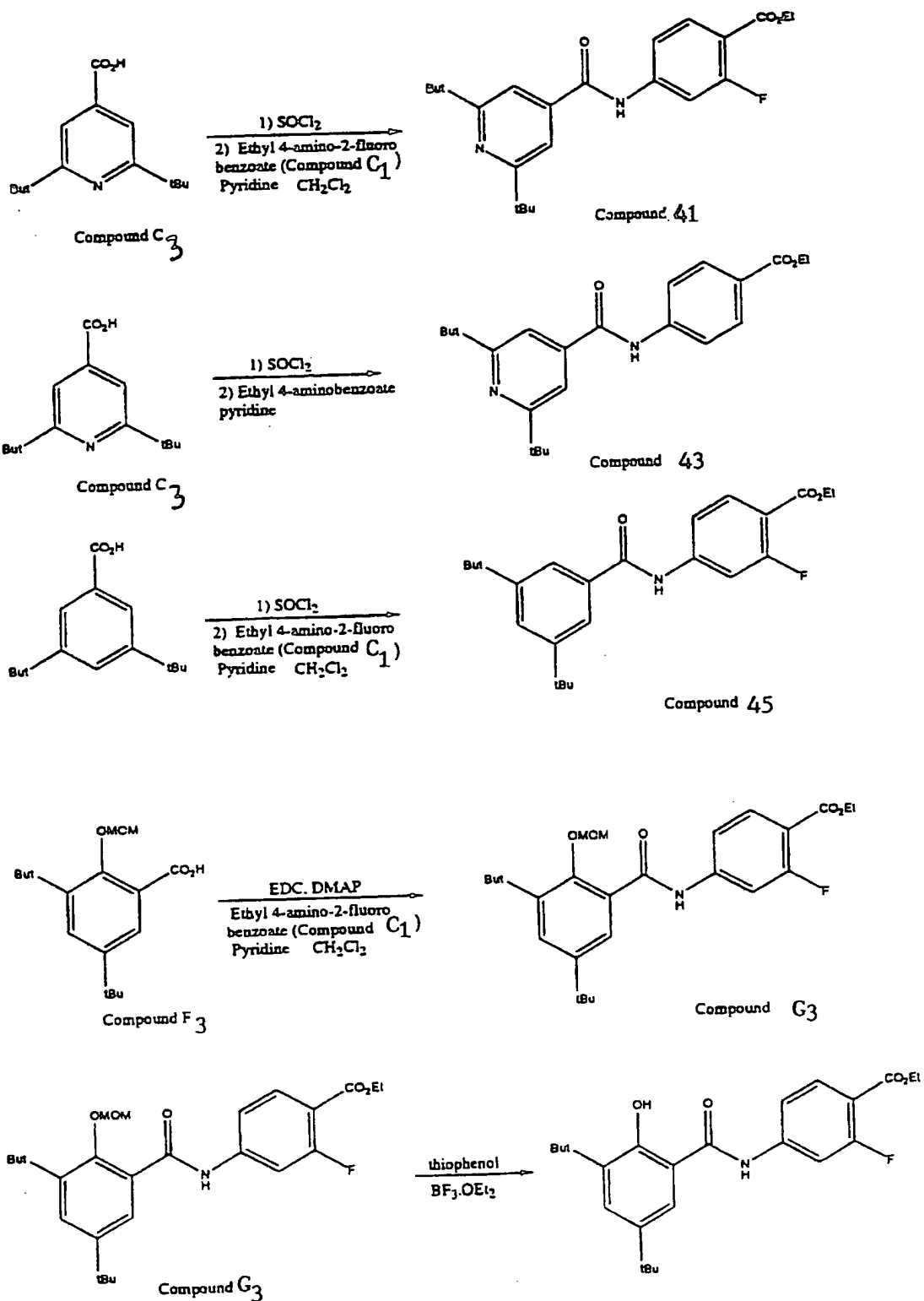
1 thereafter oxidized in a Jones oxidation reaction to
2 give 2,6-di-tert-butylisonicotinic acid (Compound
3 C₃).



Reaction Scheme 13

1 A further example of a compound which serves as
2 a reagent for preparing the carbamoyl (or amide)
3 compounds of the present invention is provided in
4 Reaction Scheme 13. 2,4-Di-tert-butylphenol
5 (Aldrich) is brominated in glacial acetic acid to
6 yield 2-bromo-4,6-di-tert-butylphenol (Compound D,)
7 which is thereafter reacted with methoxymethyl
8 chloride (MOMCl) to give
9 O-methoxymethyl-2-bromo-4,6-di-tert-butylphenol
10 (Compound E,). Compound E, is treated with t-butyl
11 lithium followed by carbon dioxide to yield
12 O-methoxymethyl-3,5-di-tert-butylsalicylic acid
13 (Compound F,). Compound F, is a reagent which
14 differs from the compounds generally encompassed by
15 Formula 8 only in that the hydroxyl function of this
16 compound is protected by the methoxymethyl (MOM)
17 group. However, the methoxymethyl protecting group
18 is removed after formation of the carbamoyl (amide)
19 linkage, as exemplified in Reaction Scheme 14.
20 Reaction of an aromatic bromo compound (such as
21 Compound D,) with t-butyl lithium followed by carbon
22 dioxide is a preferred method for preparing several
23 aromatic carboxylic acids in accordance with Formula
24 8 and Formula 7a, described in the present
25 application.

26 The primary amine compounds of Formula 8a which
27 are not available commercially or by a published
28 literature procedure can be made from the acid
29 chlorides ($X_1 = Cl$) or other form of activated acids
30 of Formula 8 substantially in accordance with the
31 steps of a Curtius rearrangement, in analogy to the
32 reaction steps described above in connection with
33 Reaction Scheme 11.



Reaction Scheme 14

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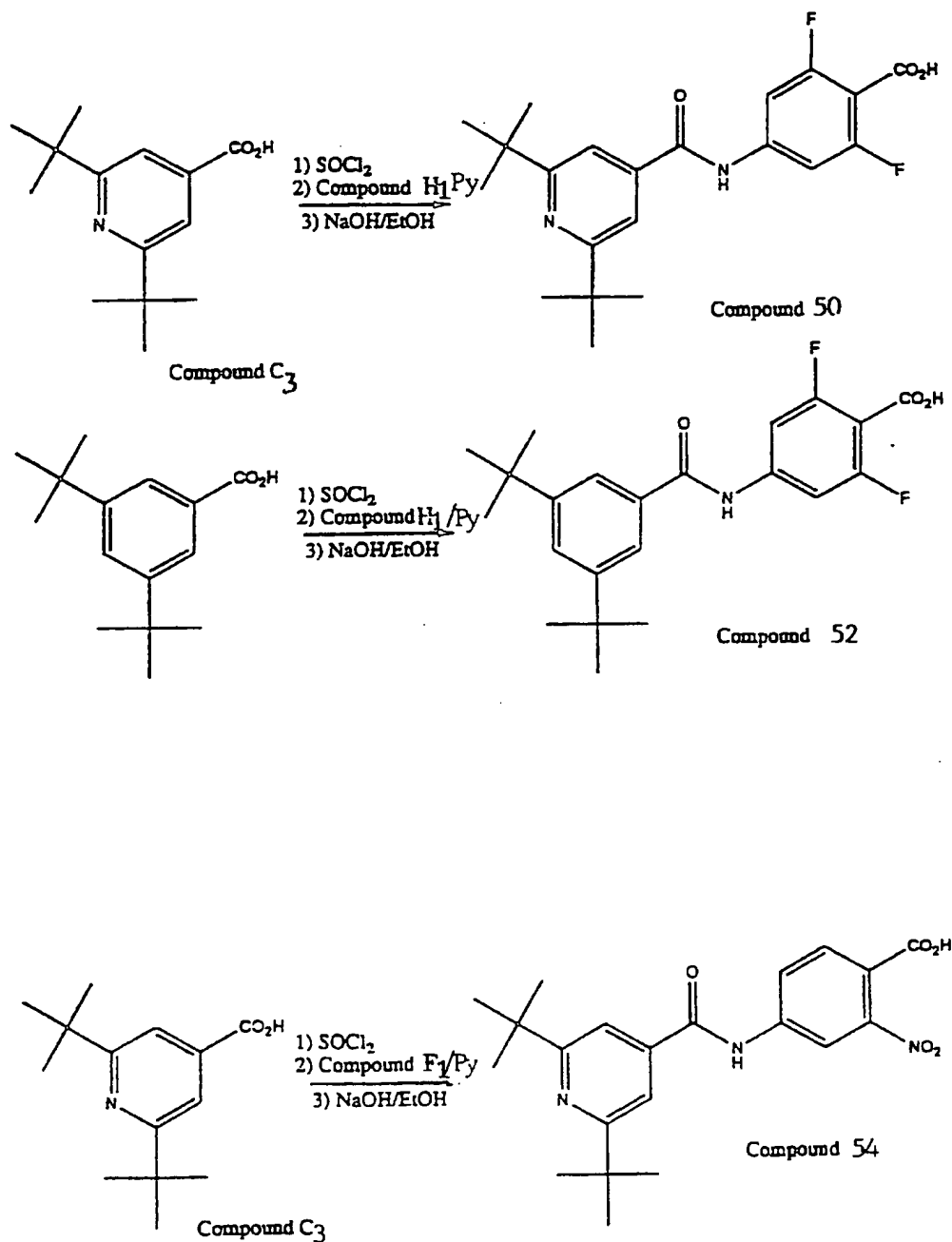
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Reaction Scheme 14 (continued)

1 Reaction Scheme 14 illustrates examples for the
2 formation of the carbamoyl (amide) compounds in
3 accordance with Formula 2, by reaction of a reagent
4 of Formula 8 with a reagent of Formula 7. Thus,
5 2,6-di-tert-butylisonicotinic acid (Compound C₃) is
6 reacted with thionyl chloride (SOCl₂) to provide the
7 intermediate acid chloride, which is then reacted
8 with ethyl 2-fluoro-4-amino-benzoate (Compound C₁) in
9 the presence of an acid acceptor (pyridine) to yield
10 ethyl 2-fluoro-4-[(2',6'-di-tert-butylpyrid-4'-
11 yl)carbamoyl]benzoate (Compound 41). As another
12 example, 3,5-di-tert-butylbenzoic acid (available by
13 the literature procedure of Kagechika et al., J.
14 Med. Chem. 1988, 31, 2182, incorporated herein by
15 reference) is reacted with thionyl chloride,
16 followed by ethyl 2-fluoro-4-amino-benzoate
17 (Compound C₁) to yield ethyl 2-fluoro-4-[(3',5'-di-
18 tert-butylphenyl)carbamoyl]benzoate (Compound 45).
19 As still another example, O-methoxymethyl-3,5-di-
20 tert-butylsalicylic acid (Compound F₃) is reacted with
21 ethyl 2-fluoro-4-amino-benzoate (Compound C₁) in the
22 presence of 4-dimethylaminopyridine (DMAP) catalyst
23 and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
24 hydrochloride (EDC) to give ethyl 2-fluoro-4-[(2'-
25 methoxymethyl-3',5'-di-tert-butylphenyl)car-
26 bamoyl]benzoate (Compound G₃). The methoxymethyl
27 protecting group is removed from Compound G₃ by
28 treatment with borontrifluoride etherate and
29 thiophenol to yield ethyl 2-fluoro-4-[(2'-hydroxy-
30 3',5'-di-tert-butylphenyl)carbamoyl]benzoate
31 (Compound 47).

32 In yet another example shown in Reaction Scheme
33 14, 2,6-di-tert-butylisonicotinic acid (Compound C₃)
34 is reacted with thionyl chloride (SOCl₂), the

1 resulting intermediate acid chloride is reacted with
2 methyl 2,6-difluoro-4-amino benzoate (Compound E₁),
3 followed by saponification of the ester group, to
4 yield 2,6-difluoro-4-[(2',6'-di-tert-butylpyrid-
5 4'yl)carbamoyl]benzoic acid (Compound 50).
6 3,5-Di-tert-butylbenzoic acid is subjected to the
7 same sequence of reactions to provide
8 2,6-difluoro-4-[(3',5'-di-tert-butylphenyl)car-
9 bamoyl]benzoic acid (Compound 52).

10 As yet another example, shown in Reaction Scheme
11 14, 2,6-di-tert-butylisonicotinic acid (Compound C₃)
12 is reacted with thionyl chloride (SOCl₂), followed by
13 methyl 2-nitro-4-aminobenzoate (Compound F₁) and
14 saponification of the ester function to give
15 2-nitro-4-[(2',6'-di-tert-butylpyrid-4'-yl)carbamoyl
16]benzoic acid (Compound 54).

17 Numerous other reactions suitable for preparing
18 compounds of the invention, and for converting
19 compounds of Formula 1 and/or of Formula 2 into
20 still further compounds which can be used in the
21 methods of treatment of the present invention, and
22 also for preparing the reagents of Formula 6,
23 Formula 7, Formula 8, Formula 6a, Formula 7a and
24 Formula 8a will become readily apparent to those
25 skilled in the art in light of the present
26 disclosure. In this regard the following general
27 synthetic methodology, applicable for conversion of
28 the compounds of Formula 1 and/or of Formula 2 into
29 further homologs and/or derivatives, and also for
30 preparing the reagents of Formula 6, Formula 7, and
31 8, (as well as 6a, 7a and 8a) is noted.

32 Carboxylic acids are typically esterified by
33 refluxing the acid in a solution of the appropriate
34 alcohol in the presence of an acid catalyst such as

1 hydrogen chloride or thionyl chloride.
2 Alternatively, the carboxylic acid can be condensed
3 with the appropriate alcohol in the presence of
4 dicyclohexylcarbodiimide and dimethylaminopyridine.
5 The ester is recovered and purified by conventional
6 means. Acetals and ketals are readily made by the
7 method described in March, "Advanced Organic
8 Chemistry," 2nd Edition, McGraw-Hill Book Company, p
9 810). Alcohols, aldehydes and ketones all may be
10 protected by forming respectively, ethers and
11 esters, acetals or ketals by known methods such as
12 those described in McOmie, Plenum Publishing Press,
13 1973 and Protecting Groups, Ed. Greene, John Wiley &
14 Sons, 1981.

15 The acids and salts derived from compounds of
16 Formula 1 and Formula 2 are readily obtainable from
17 the corresponding esters. Basic saponification with
18 an alkali metal base will provide the acid. For
19 example, an ester may be dissolved in a polar
20 solvent such as an alkanol, preferably under an
21 inert atmosphere at room temperature, with about a
22 three molar excess of base, for example, potassium
23 or lithium hydroxide. The solution is stirred for
24 an extended period of time, between 15 and 20 hours,
25 cooled, acidified and the hydrolysate recovered by
26 conventional means.

27 The amide (in Formula 1 or 2 B is CONR_1R_2) may
28 be formed by any appropriate amidation means known
29 in the art from the corresponding esters or
30 carboxylic acids. One way to prepare such compounds
31 is to convert an acid to an acid chloride and then
32 treat that compound with ammonium hydroxide or an
33 appropriate amine.

34 Alcohols are made by converting the

1 corresponding acids to the acid chloride with
2 thionyl chloride or other means (J. March, "Advanced
3 Organic Chemistry", 2nd Edition, McGraw-Hill Book
4 Company), then reducing the acid chloride with
5 sodium borohydride (March, Ibid, pg. 1124), which
6 gives the corresponding alcohols. Alternatively,
7 esters may be reduced with lithium aluminum hydride
8 at reduced temperatures. Alkylating these alcohols
9 with appropriate alkyl halides under Williamson
10 reaction conditions (March, Ibid, pg. 357) gives the
11 corresponding ethers. These alcohols can be
12 converted to esters by reacting them with
13 appropriate acids in the presence of acid catalysts
14 or dicyclohexylcarbodiimide and
15 dimethylaminopyridine.

16 Aldehydes can be prepared from the corresponding
17 primary alcohols using mild oxidizing agents such as
18 pyridinium dichromate in methylene chloride (Corey,
19 E. J., Schmidt, G., Tet. Lett., 399, 1979), or
20 dimethyl sulfoxide/oxalyl chloride in methylene
21 chloride (Omura, K., Swern, D., Tetrahedron, 1978,
22 34, 1651).

23 Ketones can be prepared from an appropriate
24 aldehyde by treating the aldehyde with an alkyl
25 Grignard reagent or similar reagent followed by
26 oxidation.

27 Acetals or ketals can be prepared from the
28 corresponding aldehyde or ketone by the method
29 described in March, Ibid, p 810.

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Specific ExamplesEthyl 4-Amino-2-fluorobenzoate (Compound C₁)

To a mixture of 2-fluoro-4-nitrotoluene (1.0 g, 6.4 mmol, Aldrich) and Na₂Cr₂O₇ (2.74 g, 8.4 mmol) in 13.7 ml of HOAc was added slowly 6.83 ml of H₂SO₄. This mixture was slowly heated to 90 °C for 1 h to give a greenish heterogeneous solution. The mixture was cooled to room temperature and diluted with ethyl acetate. The PH of the solution was adjusted to 4 with NaOH (aq.). The mixture was extracted with more ethyl acetate. The organic layer was washed with NaHCO₃ (sat.), then brine and dried over Na₂SO₄. After filtration, the solution was concentrated to dryness which then was dissolved in 6 ml of SOCl₂, and heated at 80 °C for 1 h. The excess of SOCl₂ was removed under reduced pressure and the residue was dissolved in 5 ml of CH₂Cl₂, 2 ml of EtOH and 2 ml of pyridine. The mixture was stirred at room temperature for 2 h and concentrated to dryness. Ethyl 2-fluoro-4-nitrobenzoate was obtained as a white solid after column chromatography of the residue with ethyl acetate/hexane (1/9). This solid was then dissolved in 10 ml of ethyl acetate, and Pd/C (50 mg) was added. Hydrogenation with a hydrogen balloon converted ethyl 2-fluoro-4-nitrobenzoate into the title compound.

¹H NMR δ 7.77 (t, J = 8.4 Hz, 1H), 6.41 (dd, J₁ = 8.6, J₂ = 2.2 Hz, 1H), 6.33 (dd, J₁ = 13.0, J₂ = 2.2 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 4.3 (b, 2H), 1.37 (t, J = 7.1 Hz, 3H).

Methyl 4-Amino-2,6-difluorobenzoate (Compound E₁)

A solution of trifluorobenzoic acid (150 mg, 0.85 mmol, Aldrich) in 0.5 ml of SOCl₂ was heated

1 under reflux for 2h. The reaction mixture was
2 cooled to room temperatur , and excess of SOCl₂ was
3 removed under reduced pressure. The residue was
4 dissolved in 1 ml of pyridine and 0.2 ml of
5 methanol. After stirring at room temperature for 30
6 min, solvent was removed and the residue was
7 purified by column chromatography (ethyl
8 acetate/hexane 1/10) to give methyl trifluoro-
9 benzoate as a colorless oil. This oil was then
10 dissolved in 1 ml of CH₃CN, then a solution of NaN₃
11 (100 mg, 1.54 mmol) in 0.5 ml of water was added.
12 The reaction mixture was refluxed for two days.
13 Salt was filtered and the remaining solution was
14 concentrated to an oil. This oil was then dissolved
15 in 1 ml of methanol, followed by a catalytic amount
16 of Pd/C (10%, w/w). The reaction mixture was
17 hydrogenated under a hydrogen balloon for 12 h.
18 Catalyst was removed and the solution was
19 concentrated to an oil. After column chromatography
20 (ethyl acetate/hexane 1/3), the title product was
21 obtained as colorless crystals.
22 ¹H NMR δ 6.17 (d, J = 10.44 Hz, 2H), 4.2 (b, 2H),
23 3.87 (s, 3H).

24 8-Bromo-2,2,4,4-tetramethyl-6-chromanoic acid
25 (Compound P)

26 To a solution of 2,2,4,4-tetramethyl-6-chro-
27 manoic acid (200 mg, 0.85 mmol) in 0.5 ml of AcOH
28 was added Br₂ (0.07 ml, 1.28 mmol). The resulting
29 dark-orange solution was stirred at room temperature
30 for overnight. The excess bromine was removed under
31 reduced pressure. Then the solution was poured into
32 5 ml of water and extracted with ethyl acetate
33 (3x3ml). The combined ethyl acetat layers were
34 further washed with NaHCO₃ (sat.), brine and dried

1 over MgSO_4 . After concentration, the residue was
2 purified by column chromatography (silica gel, ethyl
3 acetate/hexane 1/3) to yield the desired product
4 (170 mg, as white solids.

5 ^1H NMR δ 8.11 (d, $J = 2.2$ Hz, 1H), 8.00 (d, $J = 2.2$
6 Hz, 1H), 1.90 (s, 2H), 1.43 (s, 6H), 1.39 (s, 6H).

7 8-Iodo-2,2,4,4-tetramethyl-6-chromanoic Acid

8 (Compound X)

9 To a solution of 2,2,4,4-tetramethyl-6-chro-
10 manoic acid (66 mg, 0.28 mmol) in 0.8 ml of AcOH was
11 added ICl (0.07 ml, 1.4 mmol). The resulting
12 colored solution was stirred at room temperature for
13 overnight. Following the same procedure as for the
14 synthesis of 8-bromo-2,2,4,4-tetramethyl-6-
15 chromanoic acid (Compound P), the reaction gave the
16 title compound (107 mg) as white solids.

17 ^1H NMR δ 8.35 (d, $J = 2.2$ Hz, 1H), 8.03 (d, $J = 2.2$
18 Hz, 1H), 1.87 (s, 2H), 1.43 (s, 6H), 1.38 (s, 6H).

19 2,2,4,4-Tetramethyl-8-trifluoromethylchroman-6-oic
20 acid (Compound S)

21 A solution of 8-bromo-2,2,4,4-tetramethyl-6-
22 chromanoic acid (Compound R, 150 mg, 0.48 mmol) in 1
23 ml of SOCl_2 was refluxed for 2 h. After cooling to
24 room temperature, the excess of SOCl_2 was removed
25 under reduced pressure and the residue was dissolved
26 in 1 ml of pyridine and 0.2 ml of methanol. The
27 mixture was stirred at room temperature for 30 min.
28 Solvent was removed and the residue was passed
29 through a column (silica gel, ethyl acetate/hexane
30 1/10) to give the methyl 8-bromo-2,2,4,4-tetra-
31 methylchromanoate (158 mg) as a colorless oil. To a
32 solution of this methyl ester in 3 ml of
33 N-methylpyrrolidone (NMP) was added NaCO_2CF_3 (502 mg,
34 3.7 mmol) and CuI (350 mg, 1.84 mmol). The

1 resulting mixture was heated to 175 °C (bath temp)
2 for 2 h. The resulting mixture was cooled to room
3 temperature and poured into ice-water. The product
4 was extracted into ethyl acetate (3x3ml). The
5 combined organic layers were dried and concentrated
6 to dryness. The crude material was purified by
7 column chromatography (ethyl acetate/chloroform
8 1/10) to give the title compound as a colorless oil
9 (120 mg). This was hydrolyzed under standard
10 conditions to give the title compound.

11 ¹H NMR δ 8.21 (d, J = 2.1 Hz, 1H), 8.17 (d, J = 2.1
12 Hz, 1H), 1.92 (s, 2H), 1.41 (s, 12H).

13 Ethyl 8-Nitro-2,2,4,4-tetramethyl-6-chromanoate
14 (Compound W)

15 Ethyl 2,2,4,4-tetramethyl-6-chromanoate (150 mg,
16 0.57 mmol) was slowly added to 0.3 ml of conc. H₂SO₄
17 at 0 °C. To this mixture was added very slowly 0.03
18 ml of HNO₃. The reaction mixture was stirred at 0 °C
19 for 30 min and poured into ice-water. The product
20 was extracted into 5 ml of ethyl acetate, washed
21 with NaHCO₃ (sat.), brine and dried over MgSO₄.
22 After concentration, the product was purified by
23 column chromatography (ethyl acetate/hexane 1/10) to
24 yield 74 mg of light-yellow oil.

25 ¹H NMR δ 8.24 (d, J = 2.1 Hz, 1H), 8.17 (d, J = 2.1
26 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.95 (s, 2H),
27 1.43 (s, 6H), 1.42 (s, 6H), 1.40 (t, J = 7.1 Hz,
28 3H).

29 2-Oxo-4,4,8-trimethylchroman (Compound P₁)

30 In a 500 ml of round bottom flask, NaH (1.66 g,
31 60% suspension in oil, 0.046 mol) was washed with
32 dry hexane. Then, dry THF (22 ml) was added
33 followed by o-cresol (5 g, 0.046 mol) in 10 ml of
34 dry THF. The reaction mixture was stirred at 0 °C

1 for 30 min followed by addition of 3,3-dimethyl
2 acryloyl chloride in 10 ml of THF. The resulting
3 white slurry was stirred at room temperature for 12
4 h, then slowly quenched with water. The mixture was
5 then extracted with ethyl acetate. The organic
6 layer was washed with brine, water and dried over
7 MgSO_4 . After filtration and removal of the solvent,
8 a yellow oil was obtained (10.44 g). This oil was
9 then dissolved in 50 ml of dry CH_2Cl_2 , and was
10 canulated into a solution of AlCl_3 (10.8 g, 0.069
11 mmol) in 10 ml of CH_2Cl_2 . The reaction mixture was
12 stirred at room temperature for 12 h. Then
13 ice-water was carefully added and the organic layer
14 was separated, and washed with NaHCO_3 (sat), brine,
15 water and finally dried over MgSO_4 . After removal of
16 the drying agent and solvent, the residue was
17 purified by column chromatography (silica gel, ethyl
18 acetate/hexane 1/9) to yield the title compound
19 (4.408 g) as an oil.
20 ^1H NMR δ 7.1 (m, 3H), 2.62 (s, 2H), 2.33 (s, 3H),
21 1.36 (s, 6H).

22 2,4-Dimethyl-4-(2'-hydroxy-3'-methylphenyl)pentan-2-
23 ol (Compound R₁)

24 To a solution of 2-oxo-4,4,8-trimethylchroman
25 (Compound P₁, 2.20 g, 11.5 mmol) in 40 ml of dry
26 ethyl ether was added methyl magnesium bromide
27 (12.67 ml, 38 mmol, 3 M solution in THF). The
28 reaction mixture was stirred at room temperature for
29 12 h, then quenched with NH_4Cl (sat.) until all
30 precipitate dissolved. The mixture was extracted
31 with diethyl ether and the combined organic layers
32 were separated and washed with brine, water and
33 dried over MgSO_4 . After filtration and removal of
34 the solvent, the title compound was obtained as a

1 tan solid (2.215 g).

2 ^1H NMR δ 7.16 (d, $J = 7.88$ Hz, 1H), 7.00 (d, $J = 6.72$
3 Hz, 1H), 6.81 (t, $J = 7.6$ Hz, 1H), 5.89 (b, 1H),
4 2.21 (s, 3H), 2.17 (s, 2H), 1.48 (s, 6H), 1.10 (s,
5 6H).

6 2, 2, 4, 4, 8-Pentamethyl-6-bromochroman (Compound
7 Z) A solution of 2,4-dimethyl-4-(2'-hydroxy-3'-
8 methylphenyl)pentan-2-ol (Compound R₁, 2.215 g, 9.98
9 mmol) in 30 ml of 15% of H_2SO_4 was heated to 110 °C.
10 After cooling to room temperature, the reaction
11 mixture was extracted with diethyl ether. The
12 organic layer was washed with NaHCO_3 (sat.), brine
13 and water. After filtration and removal of solvent,
14 the residue was passed through a column (silica gel,
15 pure hexane) to give the title compound as a clear
16 oil (1.636 g). This oil was then dissolved in 1.5
17 ml of HOAc, then Br_2 (0.4113 ml, 7.98 mmol) was
18 added. The reaction mixture was stirred at room
19 temperature for 12 h. Solvent was removed under
20 reduced pressure and to the residue was added ethyl
21 acetate, and the resulting mixture was washed with
22 NaHCO_3 (sat.), brine, water and dried over MgSO_4 .
23 After filtration and removal of solvent, the residue
24 was passed through a column (silica gel, pure
25 hexane) to give the title compound as a white solid
26 (2.227 g).

27 ^1H NMR δ 7.21 (s, 1H), 7.06 (s, 1H), 2.14 (s, 3H),
28 1.79 (s, 2H), 1.32 (s, 6H), 1.31 (s, 6H).

29 2,2,4,4,8-Pentamethyl-6-chromanoic Acid (Compound A₁)

30 To a solution of 2,2,4,4, 8-pentamethyl-6-bromo-
31 chroman (Compound Z) (1.2 g, 4.24 mmol) in 18 ml of
32 dry THF at -78 °C under argon gas was added slowly
33 5.48 ml of t-BuLi (1.7 M in hexane, 9.33 mmol). The
34 reaction mixture was stirred at -78 °C for 1 h. Then

1 CO₂ was bubbled through the solution for 1 h. After
2 removal of CO₂ stream, the reaction mixture was
3 stirred for an additional hour at -78 °C. Then 10%
4 of HCl was added. After warming up to room
5 temperature, the reaction mixture was extracted with
6 ethyl acetate. The organic layer was further washed
7 with brine and dried over Na₂SO₄. After
8 concentration, the residue was purified by column
9 chromatography (ethyl acetate/hexane 5/95) to yield
10 the title compound as a white solid (774 mg).

11 ¹H NMR δ 7.96 (s, 1H), 7.75 (s, 1H), 2.23 (s, 3H),
12 1.88 (s, 2H), 1.39 (s, 6H).

13 8-Bromo-4,4-dimethyl-6-chromanoic Acid (Compound B₁)

14 Using the same procedure as for the synthesis of
15 8-bromo-2,2,4,4-tetramethylchromanoic acid (Compound
16 P) but using 4,4-dimethylchromanoic acid (100 mg,
17 0.49 mmol), the title compound was obtained as a
18 white solid.

19 ¹H NMR δ 8.10 (d, J = 2.1 Hz, 1H), 7.98 (d, J = 2.1
20 Hz, 1H), 4.39 (t, J = 5.44 Hz, 2H), 1.89 (t, J = 5.4
21 Hz, 1H), 1.38 (s, 6H).

22 Ethyl 2-Amino-1-bromo-5,5,8,8-tetrahydro-5,5,8,8-
23 tetramethylnaphthalene-3-carboxylate (Compound D)

24 To a solution of ethyl 5,6,7,8-tetrahydro-
25 5,5,8,8-tetramethyl-3-aminonaphthalene-2-carboxylate
26 (Compound C, 58 mg, 0.21 mmol) in 2 ml of HOAc was
27 added Br₂ (0.02 ml, 0.42 mmol). The orange solution
28 was stirred at room temperature for 2 days. The
29 excess Br₂ and HOAc were removed under reduced
30 pressure and the residue was passed through a column
31 (silica gel, ethyl acetate/hexane 1/10) to yield the
32 title compound as a light-orange oil (59 mg, 79.5%).
33 ¹H NMR δ 7.90 (s, 1H), 6.41 (b, 2H), 4.36 (q, J = 7.2
34 Hz, 2H), 1.70 (m, 4H), 1.58 (s, 6H), 1.40 (t, J =

1 7.2 Hz, 3H), 1.28 (s, 6H).

2 Ethyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl
3 -4-bromonaphthalene-2-carboxylate (Compound E)

4 Ethyl 2-Amino-1-bromo-5,5,8,8-tetrahydro-
5 5,5,8,8-tetramethylnaphthalene-3-carboxylate
6 (Compound D, 59 mg, 0.17 mmol) was dissolved in 2 ml
7 of EtOH at 0°C. To this solution was added 1ml of
8 trifluoroacetic acid and 1 ml of isoamylnitrite.
9 The reaction mixture was stirred at 0°C for 30 min
10 then H₃PO₂ (0.325 ml, 3.14 mmol) was added. The
11 reaction mixture was allowed to warm to room
12 temperature and stirred for 12 h. NaHCO₃ (sat.) was
13 added and the reaction mixture was extracted with
14 ethyl acetate, dried over MgSO₄, filtered and
15 concentrated to give an oil. The product was
16 purified by column chromatography (silica gel, ethyl
17 acetate/hexane 1/10) to give the title compound as a
18 colorless oil.

19 ¹H NMR δ 8.02 (d, J = 2.0 Hz, 1H), 7.95 (d, J = 2.0
20 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.71 (m, 4H),
21 1.56 (s, 6H), 1.38 (t, J = 7.1 Hz, 3H), 1.31 (s,
22 6H).

23 Ethyl

24 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-fluoro-
25 naphthalen-2-yl-carboxylate (Compound G)

26 In an ice bath, ethyl
27 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-aminonaphth
28 alene-2-carboxylate (Compound C, 150 mg, 0.55 mmol)
29 was added 0.24 ml of HBF₄ (48% solution in water),
30 followed by a solution of NaNO₂ (81 mg, 1.16 mmol) in
31 1 ml of water. The slurry was left in a
32 refrigerator for 3 days. The reaction mixture was
33 washed successively with ethyl acetate until TLC
34 showed no UV visible spot at the baseline. The

1 thyl acetate layer was dried with MgSO_4 and th
2 solution was concentrated to an oil. The oil was
3 further dissolved in 1 ml of toluene and the mixture
4 was heated under reflux for 2 h. After the reaction
5 cooled to room temperature, solvent was evaporated
6 and the residue was passed through a column (silica
7 gel, ethyl acetate/hexane 1/10) to give the title
8 compound as an oil.

9 ^1H NMR δ 7.85 (d, $J = 7.8$ Hz, 1H), 7.04 (d, $J = 12.3$
10 Hz, 1H), 4.38 (q, $J = 7.1$ Hz, 2H), 1.69 (s, 4H),
11 1.38 (t, $J = 7.1$ Hz, 3H), 1.30 (s, 6H), 1.28 (s,
12 6H).

13 2-Bromo-3-hydroxy-5,5,8,8-tetrahydro-5,5,8,8-tetrame
14 thylnaphthalene (Compound I)

15 Using the same procedure as for the synthesis of
16 8-bromo-2,2,4,4-tetramethyl-6-chromanoic acid
17 (Compound P) but using 2-hydroxy-5,5,8,8-tetrahydro-
18 5,5,8,8-tetramethyltetralin (700 mg, 3.43 mmol) and
19 Br_2 (0.177 ml, 3.43 mmol) in 1.5 ml of HOAc, the
20 title compound was obtained as a white solid (747
21 mg).

22 ^1H NMR δ 7.36 (s, 1H), 6.96 (s, 2H), 5.32 (b, 1H),
23 1.66 (s, 4H), 1.25 (s, 12H).

24 5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-3-methoxymet-
25 hoxy-2-bromonaphthalene (Compound J)

26 To a solution of 2-bromo-3-hydroxy-5,5,8,8-tet-
27 rahydro-5,5,8,8-tetramethylnaphthalene (Compound I,
28 600 mg, 2.12 mmol) and catalytic amount of Bu_4NBr in
29 20 ml of dry CH_2Cl_2 at 0 °C was added
30 diisopropylethylamine (1.138 ml, 12.75 mmol),
31 followed by methoxymethyl chloride (0.484 ml, 6.39
32 mmol). The reaction mixture was heated at 45 °C for
33 12 h. The reaction mixture was washed with 10% of
34 citric acid, then NaHCO_3 (sat.), brine and dried over

1 MgSO₄. After filtration and removal of the solvent,
2 the residue was purified by column chromatography
3 (ethyl acetate/hexane 1/9) to yield the title
4 compound (722 mg) as a white solid.

5 ¹H NMR δ 7.43 (s, 1H), 7.06 (s, 1H), 5.21 (s, 2H),
6 3.54 (s, 3H), 1.66 (s, 4H), 1.26 (s, 6H), 1.25 (s,
7 6H).

8 3-Methoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetra-
9 hydronaphthalen-2-yl carboxylic acid (Compound K)

10 Using the same procedure as for the synthesis of
11 2,2,4,4,8-pentamethyl-6-chromanoic acid (Compound A₁)
12 but using 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-
13 3-methoxymethoxy-2-bromonaphthalene (Compound J, 722
14 mg, 2.21 mmol) and 2.86 ml of t-BuLi (4.87 mmol, 1.7
15 M solution in hexane), the title compound was
16 obtained as a white solid (143 mg).

17 ¹H NMR δ 8.12 (s, 1H), 7.19 (s, 1H), 5.40 (s, 2H),
18 3.58 (s, 3H), 1.70 (s, 4H), 1.30 (s, 12H).

19 Ethyl 2-Fluoro-4-[(5',6',7',8'-tetrahydro-
20 5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]be-
21 nzoate (Compound 1)

22 To 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-
23 2-naphthoic acid (46 mg, 0.2 mmol) was added 1 ml
24 thionyl chloride. This mixture was refluxed for 2
25 h. Excess thionyl chloride was removed under
26 reduced pressure and the residue was dissolved in 2
27 ml of CH₂Cl₂. To this solution was added ethyl
28 4-amino-2-fluorobenzoate ((Compound C₁, 37 mg, 0.2
29 mmol) followed by 0.5 ml of pyridine. The reaction
30 mixture was stirred at room temperature for 4 h and
31 was concentrated under reduced pressure. The
32 residue was purified by column chromatography (ethyl
33 acetate/hexane 1/10) to give the title compound as
34 white solids.

1 ¹H NMR δ 8.06 (b, 1H), 7.93 (t, J = 8.4 Hz, 1H), 7.85
2 (d, J = 2.0 Hz, 1H), 7.78 (dd, J₁ = 2.0 Hz, J₂ = 12.9
3 Hz, 1H), 7.55 (dd, J₁ = 2.0 Hz, J₂ = 8.2 Hz, 1H),
4 7.40 (d, J = 8.3 Hz, 1H), 7.32 (dd, J₁ = 2.02 Hz, J₂
5 = 8.8 Hz, 1H), 4.38 (q, J = 7.2 Hz, 2H), 1.71 (s,
6 4H), 1.40 (t, J = 7.2 Hz), 1.32 (s, 6H), 1.30 (s,
7 6H).

8 Ethyl 2-Fluoro-4-[(5',6',7',8'-tetrahydro-4'-
9 bromo-5',5',8',8'-tetramethylnaphthalen-2'-yl)carbam
10 oyl]benzoate (Compound 3)

11 Using the same procedure as for the synthesis of
12 ethyl 2-fluoro-4-[-5',6',7',8'-tetrahydro-
13 5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]be
14 nzoate (Compound 1), but using
15 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-4-bromonaphth
16 alene-2-carboxylic acid (Compound F), the title
17 compound was obtained as a white solid.

18 ¹H NMR δ 8.30 (b, 1H), 7.92 (t, J = 8.4 Hz, 1H), 7.84
19 (d, J = 2.1 Hz, 1H), 7.81 (d, J = 2.1 Hz, 1H), 7.74
20 (dd, J₁ = 2.1 Hz, J₂ = 12.8 Hz, 1H), 7.35 (dd, J₁ =
21 2.0 Hz, J₂ = 8.4 Hz, 1H), 4.36 (q, J = 7.2 Hz, 2H),
22 1.67 (m, 4H), 1.55 (s, 6H), 1.39 (t, J = 7.2 Hz,
23 3H), 1.31 (s, 6H).

24 Ethyl
25 2-Fluoro-4-[(3'-methoxymethoxy-5',6',7',8'-tet-
26 rahydro-5',
27 5',8',8'-tetramethylnaphthalen-2'-yl)car-
28 bamoyl]benzoate (Compound K₁)

29 Using the same procedure as for the synthesis of
30 ethyl 2-fluoro-4-[(3'-methoxymethoxy-4'-bromo-
31 5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylnaphth
32 alen-2'-yl)carbamoyl]benzoate (Compound S₁), but
33 using 3-methoxymethoxy-5,5,8,8-tetramethyl-
34 5,6,7,8-tetrahydronaphthalen-2-yl carboxylic acid

1 (Compound K, 143 mg, 0.49 mmol) and
2 4-amino-2-fluorobenzoate (Compound C₁, 98.5 mg, 0.54
3 mmol), the title compound was obtained as a white
4 solid.
5 ¹H NMR δ 10.1 (b, 1H), 8.20 (s, 1H), 7.93 (t, J = 8.8
6 Hz, 1H), 7.83 (d, J = 13.4 Hz, 1H), 7.29 (d, J = 8.0
7 Hz, 1H), 5.41 (s, 2H), 4.39 (q, J = 7.1 Hz, 2H),
8 3.59 (s, 3H), 1.70 (s, 4H), 1.31 (s, 12H), 1.26 (t,
9 J = 7.1 Hz, 3H).

10 Ethyl 2-Fluoro-4-[(3'-hydroxy-5',6',7',8'-
11 tetrahydro-5',5',8',8'-tetramethyl-2-
12 naphthalenyl)carbamoyl]benzoate (Compound 5)

13 A solution of ethyl 2-fluoro-4-[(3'-methoxymet-
14 hoxy-5',6',7',8'-tetrahydro-5',
15 5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]
16 benzoate (Compound K₁, 50.7 mg, 0.11 mmol) in 2 ml of
17 CH₂Cl₂ was added thiophenol (0.061 ml, 0.55 mmol).
18 The reaction mixture was stirred at 0 °C for 5 min,
19 then BF₃·Et₂O (0.027 ml, 0.22 mmol) was added. The
20 reaction mixture was stirred at 0 °C for 2 h, then
21 NaHCO₃ (sat.) was added. The organic layer was
22 separated, and washed with brine, water and dried
23 over MgSO₄. After filtration and removal of solvent,
24 the residue was passed through a column (silica gel,
25 ethyl acetate/hexane 1/3) to give the title compound
26 as white solid (44.2 mg).

27 ¹H NMR δ 8.61 (b, 1H), 7.94 (t, J = 8.42 Hz, 1H),
28 7.71 (dd, J = 10.8, 2.0 Hz, 1H), 7.53 (s, 1H), 7.35
29 (dd, J = 6.4, 2.0 Hz, 1H), 6.96 (s, 1H), 4.39 (q, J
30 = 7.1 Hz, 2H), 1.69 (s, 4H), 1.40 (t, J = 7.1 Hz,
31 3H), 1.29 (s, 6H), 1.27 (s, 6H).

32 Ethyl 2-Fluoro-4-[(4',4'-dimethyl-8'-bromochroman-
33 6'-yl)carbamoyl]benzoate (Compound 7)

34 In a 10 ml of round bottom flask,

1 4,4-dimethyl-8-bromo-6-chromanoic acid (Compound B₁,
2 139 mg, 0.485 mmol) was added SOCl₂ (1 ml, large
3 excess). The resulting solution was heated at 90 °C
4 for 2 h and allowed to cool to room temperature.
5 The excess of SOCl₂ was evaporated under reduced
6 pressure. The residue was dissolved in CH₂Cl₂ (3
7 ml). Ethyl 4-amino-2-fluorobenzoate (Compound C₁, 90
8 mg, 0.49 mmol) was added followed by pyridine (0.5
9 ml, large excess). The reaction mixture was stirred
10 for overnight and then concentrated to dryness. The
11 residue was purified by column chromatography with
12 ethyl acetate/hexane (1/5) to yield the title
13 compound as a white solid (190 mg).

14 ¹H NMR δ 7.95 (t, J = 8.31 Hz, 1H), 7.88 (b, 1H),
15 7.83 (d, J = 2.2 Hz, 1H), 7.80 (d, J = 2.2 Hz, 1H),
16 7.75 (dd, J = 12.89, 2.0 Hz, 1H), 7.30 (dd, J =
17 8.55, 2.0 Hz, 1H), 4.37 (m, 5H), 1.89 (t, J = 5.49
18 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H), 1.39 (s, 6H).

19 Ethyl 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-bromo-
20 chroman-6'-yl)carbamoyl]benzoate (Compound 9)

21 Using the same procedure as for ethyl
22 2-fluoro-4-[(4',4'-dimethyl-8'-bromochroman-6'-yl)ca
23 rbamoyl]benzoate (Compound 7), but using
24 2,2,4,4-tetramethyl-8-bromo-6-chromanoic acid
25 (Compound P, 70 mg, 0.22 mmol) and ethyl
26 4-amino-2-fluorobenzoate (Compound C₁, 38 mg, 0.22
27 mmol), the title compound was obtained as a white
28 solid (80 mg, 76%).

29 ¹H NMR δ 8.25 (b, 1H), 7.92 (t, J = 8.4 Hz, 1H),
30 7.83 (s, 2H), 7.74 (dd, J₁ = 2.0, J₂ = 13.0 Hz, 1H),
31 7.34 (dd, J₁ = 2.0, J₂ = 8.7 Hz, 1H), 4.37 (q, J =
32 7.1 Hz, 2H), 1.88 (s, 2H), 1.41 (s, 6H), 1.39 (t, J
33 = 7.1 Hz, 3H), 1.37 (s, 6H).

34 Ethyl

1 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-trifluoromet
2 hylchroman-6'-yl)carbamoyl] benzoate (Compound 11)

3 Using the same procedure as for ethyl
4 2-fluoro-4-[(4',4'-dimethyl-8'-bromochroman-6'-yl)ca
5 rbamoyl]benzoate (Compound 7), but using
6 2,2,4,4-tetramethyl-8-trifluoromethyl-6-chromanoic
7 acid (Compound S, 57 mg, 0.19 mmol) and ethyl
8 4-amino-2-fluorobenzoate (Compound C₁, 35 mg, 0.19
9 mmol), the title compound was obtained as white
10 solids.

11 ¹H NMR δ 8.06 (d, J = 2.2 Hz, 1H), 7.99 (b, 1H), 7.95
12 (t, J = 8.55 Hz, 1H), 7.81 (d, J = 2.2 Hz, 1H), 7.76
13 (dd, J = 12.8, 2.1 Hz, 1H), 7.33 (dd, J = 8.55, 1.9
14 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 1.93 (s, 2H),
15 1.41 (s, 12H), 1.40 (t, J = 7.2 Hz, 3H). Ethyl
16 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-amino-
17 chroman-6'-yl)carbamoyl]benzoate (Compound N₁)

18 Using 8-nitro-2, 2, 4,
19 4-tetramethylchroman-6-carboxylic acid (Compound V)
20 and following the same procedure as for the
21 synthesis of ethyl 2-fluoro-4-[(4',4'-dimethyl-
22 8'-bromochroman-6'-yl)carbamoyl]benzoate (Compound
23 7), ethyl 2-fluoro-4-[(2',2',4',4'-tetramethyl-
24 8'-nitrochroman-6'-yl)]carbamoylbenzoate was
25 obtained as a white solid. This compound (50 mg,
26 0.12 mmol) was dissolved in 2 ml of methanol. A
27 catalytic amount of Pd/C was added to the solution
28 and the solution was maintained under H₂ atmosphere
29 (hydrogen balloon) for overnight. The catalyst was
30 removed by filtration and the solvent was evaporated
31 to give the title compound as a white solid.

32 ¹H NMR δ 7.93 (t, J = 8.43 Hz, 1H), 7.90 (b, 1H),
33 7.73 (dd, J = 12.9, 2.0 Hz, 1H), 7.29 (dd, J = 8.43,
34 1.96 Hz, 1H), 7.23 (d, J = 2.14 Hz, 1H), 7.01 (d, J

1 = 2.2 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.88 (s,
2 2H), 1.39 (s, 6H), 1.38 (t, J = 7.1 Hz, 3H), 1.37
3 (s, 6H).

4 Ethyl 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-
5 azidochroman-6'-yl)carbamoyl]benzoate (Compound 13)

6 To a solution of ethyl
7 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-aminochroman
8 -6'-yl)carbamoyl]benzoate (Compound N₁, 32 mg, 0.077
9 mmol) in 3 ml of EtOH was added 0.5 ml of
10 trifluoroacetic acid (TFA) and 0.5 ml of
11 isoamylnitrite at 0°C. The reaction was stirred for
12 2 h when a solution of NaN₃ (5 mg,) in 0.2 ml of
13 water was added. The reaction mixture was allowed
14 to warm to room temperature and stirred for
15 overnight. The solvent was removed and the residue
16 was purified by column chromatography (silica gel,
17 ethyl acetate/ hexane 1/10) to give the title
18 compound as a colorless oil.

19 ¹H NMR δ 8.0 (b, 1H), 7.94 (t, J = 7.8 Hz, 1H), 7.73
20 (d, J = 12.1 Hz, 1H), 7.64 (s, 1H), 7.31 (dd, J =
21 8.5, 2.0 Hz, 1H), 7.21 (d, J = 2.0 Hz, 1H), 4.37 (q,
22 J = 7.1 Hz, 2H), 1.90 (s, 2H), 1.39 (t, J = 7.1 Hz,
23 3H), 1.45 (s, 6H), 1.40 (s, 6H).

24 Methyl

25 2,6-Difluoro-4-[(2',2',4',4'-tetramethyl-8'-trifluor
26 omethylchroman-6'-yl)carbamoyl]benzoate (Compound
27 15)

28 Using the same procedure as for ethyl
29 2-fluoro-4-[(4',4'-dimethyl-8'-bromochroman-6'-yl)ca
30 rbamoyl]benzoate (Compound 7), but using
31 2,2,4,4-tetramethyl-8-trifluoromethylchromanoic acid
32 (Compound S, 11.2 mg, 0.037 mmol) and methyl
33 4-amino-2,6-difluorobenzoate (Compound H₁, 6.6 mg,
34 0.035 mmol), the title compound was obtained as

1 white crystals.

2 ¹H NMR δ 8.21 (b, 1H), 8.05 (s, 1H), 7.82 (s, 1H),
3 7.36 (d, J = 10.20 Hz, 1H), 3.93 (s, 3H), 1.92 (s,
4 2H), 1.40 (s, 12H).

5 Ethyl 2-Fluoro-4-[(2', 2', 4',
6 4'-tetramethyl-8'-iodochroman-6'-yl)carbamoyl]benzoa
7 te (Compound 17)

8 Using the same procedure as for ethyl
9 2-fluoro-4-[(4', 4'-dimethyl-8'-bromochroman-6'-yl)ca
10 rbamoyl]benzoate (Compound 7), but using
11 2,2,4,4-tetramethyl-8-iodochromanoic acid (Compound
12 X, 81 mg, 0.25 mmol) and ethyl 4-amino-2-
13 fluorobenzoate ((Compound C₁, 55 mg, 0.30 mmol), the
14 title compound was obtained as a white solid.

15 ¹H NMR δ 8.05 (b, 1H), 8.01 (d, J = 2.2 Hz, 1H), 7.94
16 (t, J = 8.4 Hz, 1H), 7.86 (d, J = 2.2 Hz, 1H), 7.75
17 (dd, J = 12.88, 2.1 Hz, 1H), 7.33 (dd, J = 8.8, 2.1
18 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 1.89 (s, 2H),
19 1.42 (s, 6H), 1.38 (s, 6H). Ethyl

20 2-Fluoro-4-[(2', 2', 4', 4', 8'-pentamethylchroman-
21 6'-yl)carbamoyl]benzoate (Compound 19)

22 Using the same procedure as for ethyl
23 2-fluoro-4-[(4', 4'-dimethyl-8'-bromochroman-6'-yl)ca
24 rbamoyl]benzoate (Compound 9), but using
25 2,2,4,4,8-pentamethyl-6-chromanoic acid (Compound
26 A₁, 92 mg, 0.37 mmol) and ethyl
27 4-amino-2-fluorobenzoate (Compound C₁, 75 mg, 0.41
28 mmol), the title compound was obtained as a white
29 solid (100 mg).

30 ¹H NMR δ 8.31 (b, 1H), 7.90 (t, J = 8.24 Hz, 1H),
31 7.76 (dd, J = 14.29, 1.7 Hz, 1H), 7.74 (s, 1H), 7.43
32 (s, 1H), 7.35 (dd, J = 8.67, 1.7 Hz, 1H), 4.32 (q, J
33 = 7.1 Hz, 2H), 2.18 (s, 3H), 1.84 (s, 2H), 1.38 (t,
34 J = 7.1 Hz, 3H), 1.35 (s, 6H), 1.34 (s, 6H).

1 Ethyl
2 4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetramethyl-2
3 -naphthalenyl)thiocarbamoyl]benzoate (Compound 21)

4 To a solution of ethyl
5 4-[(5',6',7',8'-tetrahydro-5',5',8',
6 8'-tetramethylnaphthalen-2-yl)carbamoyl]benzoate
7 (Compound I₁, 61 mg, 0.16 mmol) in 2 ml of anhydrous
8 benzene was added Lawesson's reagent (45 mg, 0.112
9 mmol). The resulting yellow solution was refluxed
10 under N₂ for 2 h. The solvent was removed and the
11 residue was purified by column chromatography
12 (silica gel, ethyl acetate/hexane 1/5) to give the
13 title compound as a yellow solid (55 mg, 87%).
14 ¹H NMR δ 9.04 (b, 1H), 8.11 (d, J = 8.70 Hz, 2H),
15 7.85 (b, 2H), 7.75 (b, 1H), 7.55 (dd, J = 8.2, 1.9
16 Hz, 1H), 7.36 (d, J = 8.3 Hz, 1H), 4.38 (q, J = 7.1
17 Hz, 2H), 1.71 (s, 4H), 1.40 (t, J = 7.1 Hz, 3H),
18 1.30 (s, 12H).

19 Ethyl 2-Fluoro-4-[(5',6',7',8'-tetrahydro-
20 5',5',8',8'-tetramethylnaphthalen-2'-yl)thiocarbamoy
21 l]benzoate (Compound 23)

22 Using the same procedure as for the synthesis of
23 ethyl 4-[(5',6',7',8'-tetrahydro-5',5',8',8'-
24 tetramethyl-2-naphthalenyl)thiocarbamoyl]benzoate
25 (Compound 21) but using ethyl
26 2-fluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetr
27 amethylnaphthalen-2'-yl)carbamoyl]benzoate (Compound
28 1, 167 mg, 0.42 mmol) in 8 ml of benzene and
29 Lawesson's reagent (220 mg, 0.544 mmol), the title
30 compound was obtained as a bright yellow solid
31 (127.5 mg).

32 ¹H NMR δ 9.30 (b, 1H), 8.05 (b, 1H), 7.95 (t, J =
33 8.37 Hz, 1H), 7.77 (d, J = 1.89 Hz, 1H), 7.53 (dd, J
34 = 8.24, 2.1 Hz, 1H), 7.49 (b, 1H), 7.35 (d, J = 8.24

1 Hz, 1H), 4.33 (q, J = 7.1 Hz, 1H), 1.71. (s, 4H),
2 1.32 (s, 6H), 1.30 (s, 6H).

3 3-Hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronap
4 hthalen-2-yl carboxylic acid (Compound L)

5 To a solution of 2-bromo-3-methoxymethoxy-
6 5,5,8,8-tetrahydro-5,5,8,8-tetramethylnaphthalene
7 (Compound J, 722 mg, 2.2 mmol) in 10 ml of dry THF
8 at -78°C under argon was added slowly 2.86 ml of
9 t-BuLi (1.7 M in hexane, 4.8 mmol). The reaction
10 mixture was stirred at -78°C for 1 h. Then CO₂ was
11 bubbled through the solution for 1 h. After removal
12 of CO₂ stream, the reaction mixture was stirred for
13 an additional hour at -78°C. Then 10% of HCl was
14 added. After warming up to room temperature, the
15 reaction mixture was left overnight then extracted
16 with ethyl acetate. The organic layer was washed
17 with brine and dried over Na₂SO₄. After
18 concentration, the residue was purified by column
19 chromatography (ethyl acetate/hexane 1/3) to yield
20 the title compound as a white solid.

21 ¹H NMR d 7.85 (s, 1H), 6.93 (s, 1H), 1.68 (s, 4H),
22 1.28 (s, 12H).

23 4-Bromo-3-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetra
24 ydronaphthalen-2-yl carboxylic acid (Compound M)

25 3-Hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-
26 naphthalen-2-yl acid (Compound L, 155 mg, 0.62 mmol)
27 was dissolved in 1 ml of HOAc. To this solution was
28 added Br₂ (0.033 ml, 0.62 mmol). The reaction
29 mixture was left at room temperature for over night.
30 A stream of air was passed through the reaction
31 mixture to remove the unreacted Br₂. The remaining
32 solid was dissolved in small amount of THF and
33 purified by column chromatography (ethyl
34 acetate/hexane 1/1) to yield the desired product as

1 a cream colored solid.

2 ¹H NMR d 7.91 (s, 1H), 1.75 (m, 2H), 1.64 (m, 2H),
3 1.62 (s, 6H), 1.30 (s, 6H).

4 4-Bromo-3-methoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8
5 -tetrahydronaphthalen-2-yl carboxylic acid (Compound
6 M)

7 To a solution of 4-bromo-3-hydroxy-5,5,8,8-
8 tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl acid
9 (Compound M), 233 mg, 0.71 mmol) in 6 ml of CH₂Cl₂,
10 was added chloromethyl methyl ether (0.162 ml, 2.1
11 mmol), diisopropylethyl amine (0.764 ml, 4.2 mmol)
12 and a catalytic amount of tetrabutylammouimn
13 bromide. The reaction mixture was heated to 45 °C
14 for 2 h. The reaction mixture was concentrated and
15 the residue was purified by column chromatography
16 (ethyl acetate/hexane 1/9) to yield the
17 methoxymethyl ester of the title compound as a white
18 solid (200 mg). This white solid was further
19 dissolved in 20 ml of EtOH. An aqueous solution of
20 NaOH (0.5 ml, 1M) was added. The reaction mixture
21 was stirred at room temperature for over night. The
22 EtOH was removed and the residue was added 2 ml of
23 ethyl acetate and 3 ml of water. This mixture was
24 very slowly acidified with 10% HCl to PH = 7. The
25 ethyl acetate layer was separated and washed with
26 brine, dried over Na₂SO₄. After filtration of the
27 drying agent and removal of solvent, the reaction
28 yielded the title compound as a white solid (155
29 mg). ¹H NMR d 7.99 (s, 1H), 5.20 (s, 2H), 3.66 (s,
30 3H), 1.74 (m, 2H), 1.67 (m, 2H), 1.60 (s, 6H), 1.32
31 (s, 6H).

32 Ethyl 2-fluoro-4-[(3'-methoxymethoxy-4'-bromo-
33 5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylnaphth
34 alen-2'-yl)carbamoyl]benzoate (Compound S₁)

1 To a solution of 4-bromo-3-methoxymethoxy-
2 5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-y
3 1 acid (Compound N, 80 mg, 0.22 mmol) in 4 ml of
4 CH₂Cl₂ was added DMAP (60 mg, 0.26 mmol), ethyl
5 2-fluoro-4-aminobenzoate (Compound C₁, 43 mg, 0.24
6 mmol) and EDC (50 mg, 0.26 mmol). The reaction
7 mixture was stirred at room temperature for
8 overnight and then concentrated to dryness. The
9 residue was purified by column chromatography (ethyl
10 acetate/hexane 1/3) to yield the title compound as a
11 clear oil (45 mg).

12 ¹H NMR d 9.92 (b, 1H), 8.10 (s, 1H), 7.94 (t, J = 8.4
13 Hz, 1H), 7.81 (dd, J = 12.9; 1.9 Hz, 1H), 7.35 (dd,
14 J = 8.5; 1.8 Hz, 1H), 5.20 (s, 2H), 4.39 (q, J =
15 7.1 Hz, 2H), 3.61 (s, 3H), 1.74 (m, 2H), 1.64 (m,
16 2H), 1.60 (s, 6H), 1.40 (t, J = 7.1 Hz, 3H), 1.34
17 (s, 6H).

18 Methyl

19 2,6-Difluoro-4-[(3'-methoxymethoxy-4'-bromo-5',6',7'
20 ,8'-tetrahydro-5',5',8',8'-tetramethylnaphtha-
21 len-2'-yl)carbamoyl]benzoate (Compound M₁)

22 Using the same procedure as for the synthesis of
23 compound ethyl 2-fluoro-4-[(3'-methoxymethoxy-4'-
24 bromo-5',6',7',8'-tetrahydro-5',5',8',8'-tetramethyl
25 naphthalen-2'-yl)carbamoyl]benzoate (Compound S₁) but
26 using 4-bromo-3-methoxymethoxy-5,5,8,8-tetramethyl-
27 5,6,7,8-tetrahydronaphthalen-2-yl acid (Compound N,
28 80 mg, 0.22 mmol), DMAP (60 mg, 0.26 mmol), methyl
29 2,6-difluoro-4-aminobenzoate (Compound H₁, 52 mg,
30 0.24 mmol) and EDC (50 mg, 0.26 mmol), the title
31 compound was obtained as a clear oil.

32 ¹H NMR d 10.01 (b, 1H), 8.11 (s, 1H), 7.42 (d, J =
33 10.0 Hz, 2H), 5.2 (s, 2H), 3.95 (s, 3H), 3.63 (s,
34 3H), 1.75 (m, 2H), 1.65 (m, 2H), 1.61 (s, 6H), 1.35

1 (s, 6H).

2 4-Bromomethyl-2,6-di-t-butylpyridine (Compound A,)

3 To a mixture of 2,6-di-t-butyl-4-methylpyridine
4 (Aldrich, 2.0 g, 9.73 mmol) in 25 ml of dry CCl₄ was
5 added benzoyl peroxide (24 mg, 0.097 mmol) and NBS
6 (1.9 g, 10.7 mmol). The reaction mixture was
7 refluxed for 16 hours. After it cooled to room
8 temperature, the solvent was removed in vacuo and
9 the residue was purified by column chromatography
10 (silica gel, hexane) to give an oil (1.957 g) which
11 contained 82% of the desired product and 18% of the
12 starting material. ¹H NMR δ 7.09 (s, 2H), 4.39 (s,
13 2H), 1.35 (s, 18H).

14 4-Hydroxymethyl-2,6-di-t-butylpyridine (Compound B,)

15 A heterogeneous solution of
16 4-bromomethyl-2,6-di-t-butylpyridine (Compound A,
17 1.743 g, 82% purity) in 20 ml of 12% NaOH in water
18 and 10 ml of 1,4-dioxane was refluxed for 12 hours.
19 The solution spontaneously separated into two layers
20 as it cooled to room temperature. The upper layer
21 was separated and ethyl acetate was added. This
22 organic layer was then washed with brine, water and
23 dried over MgSO₄. The desired product was purified
24 by column chromatography (ethyl acetate/hexane 1/9)
25 to give a white solid. ¹H NMR δ 7.09 (s, 2H), 4.67
26 (d, J = 4.4 Hz, 2H), 2.3 (b, 1H), 1.36 (s, 18H).

27 2,6-Di-t-butylisonicotinic acid (Compound C,)

28 Jone's reagent was added dropwise to a solution of
29 4-hydroxymethyl-2,6-di-t-butylpyridine (Compound B,
30 302 mg, 1.37 mmol) in 5 ml of acetone until the
31 solution changed color from light yellow to orange
32 (55 drops of Jone's reagent were consumed). After 5
33 minutes 2 ml of isopropanol were added to the
34 reaction mixture, and a green precipitate of Cr³⁺

1 salt was formed. The precipitate was removed by
2 filtration and the solution was diluted with ethyl
3 acetate, then washed with brine, water and dried
4 over MgSO_4 . After filtration, the solvent was
5 removed to give the desired product as a white solid
6 (227 mg). ^1H NMR δ 7.71 (s, 2H), 1.34 (s, 18H).

7 2-Bromo-4,6-di-*t*-butylphenol (Compound D₂)

8 To a solution of 2,4-di-*t*-butylphenol (Aldrich,
9 2.0 g, 9.7 mmol) in 2 ml of HOAc was added Br_2 (0.5
10 ml, 9.7 mmol). The reaction mixture was stirred at
11 room temperature for 12 hours. Solvent was removed
12 under reduced pressure and the residue was purified
13 by column chromatography (ethyl acetate/hexane 1/20)
14 to yield the desired product (2.54 g) as a white
15 solid. ^1H NMR δ 7.33 (d, $J = 2.3$ Hz, 1H), 7.24 (d, J
16 $= 2.3$ Hz, 1H), 1.41 (s, 9H), 1.29 (s, 9H).

17 O-Methoxymethyl-2-bromo-4,6-di-*t*-butylphenol
18 (Compound E₂)

19 To a solution of 2-bromo-4,6-di-*t*-butylphenol
20 (Compound D₂, 2.54 g, 8.88 mmol) and catalytic amount
21 of Bu_4NI in 20 ml of dry CH_2Cl_2 at 0°C was added
22 diisopropylethylamine (9.51 ml, 53 mmol), followed
23 by methoxymethyl chloride (2.02 ml, 26.6 mmol). The
24 reaction mixture was heated to 45°C for 12 hours.
25 The reaction mixture was then washed with 10% citric
26 acid, then NaHCO_3 (sat.), brine, and dried over
27 MgSO_4 . After filtration and removal of the solvent
28 under reduced pressure, the residue was purified by
29 column chromatography (pure hexane) to yield the
30 title compound (2.79 g) as a colorless oil. ^1H NMR δ
31 7.40 (d, $J = 2.44$ Hz, 1H), 7.30 (d, $J = 2.4$ Hz, 1H),
32 5.22 (s, 2H), 3.70 (s, 3H), 1.43 (s, 9H), 1.29 (s,
33 9H).

34 O-Methoxymethyl-3',5'-di-*t*-butylsalicylic acid

1 (Compound F₃)

2 To a solution of O-methoxymethyl-2-bromo-4,6-
3 di-t-butylphenol (Compound E₃, 2.79 g, 8.5 mmol) in
4 30 ml of dry THF at -78°C under Ar was added 11 ml
5 of t-BuLi (1.7 M in hexane, 18.7 mmol). This
6 mixture was stirred at -78°C for 1 hour. Then CO₂,
7 (g) was bubbled into the solution at -78°C for 1
8 hour. After removal of the CO₂ stream, the reaction
9 mixture was stirred for an additional hour at -78°C.
10 Then 10% of HCl was added and the mixture was
11 allowed to warm to room temperature and extracted
12 with ethyl acetate. The organic layer was washed
13 with brine and dried over Na₂SO₄. After
14 concentration, the residue was purified by column
15 chromatography (ethyl acetate/hexane 1/1) to yield
16 the title compound as a white solid (492 mg). ¹H NMR
17 δ 7.75 (d, J = 2.81 Hz, 1H), 7.60 (d, J = 2.8 Hz,
18 1H), 5.07 (s, 2H), 3.62 (s, 3H), 1.33 (s, 9H), 1.26
19 (s, 9H).

20 Ethyl 2-fluoro-4-[(2'6'-di-t-butylpyrid-4'-

21 yl)carbamoyl]benzoate (Compound 41)

22 A solution of 2,6-di-t-butylisonicotinic acid
23 (Compound C₃, 47.3 mg, 0.20 mmol) in 2 ml of SOCl₂
24 was heated under reflux for 2 hours. Excess SOCl₂
25 was removed in vacuo and the residue was dissolved
26 in 2 ml of dry CH₂Cl₂, and ethyl
27 2-fluoro-4-aminobenzoate (Compound C₁, 40.2 mg, 0.22
28 mmol) and pyridine (0.0835 ml, 0.69 mmol) were
29 added. The reaction mixture was stirred at room
30 temperature for 12 hours. Solvent was removed and
31 the residue was purified by column chromatography
32 (ethyl acetate/hexan 1/9) to yield the title
33 compound (71.2 mg) as white crystals. ¹H NMR δ 8.56
34 (b, 1H), 7.91 (t, J = 8.36 Hz, 1H), 7.53 (dd, J =

1 12.82, 2.0 Hz, 1H), 7.39 (dd, J = 8.7, 2.0 Hz, 1H),
2 4.33 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H),
3 1.35 (s, 18H).

4 Ethyl 4-[(2',6'-di-t-butylpyrid-4'-yl)car-
5 bamoyl]benzoate (Compound 43)

6 Using the same procedure as for the synthesis of
7 ethyl 2-fluoro-4-[(2'6'-di-t-butylpyrid-4'-
8 yl)carbamoyl]benzoate (Compound 41) but using
9 2,6-di-t-butylisonicotinic acid (Compound C₃, 101 mg,
10 0.43 mmol) and ethyl 4-aminobenzoate (78 mg, 0.47
11 mmol), the title compound was obtained as a white
12 solid (135 mg). ¹H NMR δ 8.43 (b, 1H),, 8.02 (d, J =
13 8.7 Hz, 2H), 7.75 (d, J = 8.7 Hz, 2H), 7.48 (s, 2H),
14 4.33 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H),
15 1.35 (s, 18H).

16 Ethyl
17 2-Fluoro-4-[(3',5'-di-t-butylphenyl)carbamoyl]benzoa
18 te (Compound 45)

19 Using the same procedure as for the synthesis of
20 ethyl 2-fluoro-4-[(2'6'-di-t-butylpyrid-4'-
21 yl)carbamoyl]benzoate (Compound 41) but using
22 3,5-di-t-butylbenzoic acid (60 mg, 0.26 mmol,
23 available by literature procedure, see Kagechika et
24 al. J. Med Chem. 1988 31, 2182 - 2192) and ethyl
25 2-fluoro-4-aminobenzoate (Compound C₁, 51.5 mg, 0.28
26 mmol), the title compound was obtained as a white
27 solid (66 mg). ¹H NMR δ 8.21 (b, 1H), 7.93 (t, J =
28 8.3 Hz, 1H), 7.79 (dd, J = 12.8, 2.0 Hz, 1H), 7.67
29 (d, J = 1.8 Hz, 2H), 7.65 (t, J = 1.7 Hz, 1H), 7.35
30 (dd, J = 8.7, 2.1 Hz, 1H), 4.36 (q, J = 7.2 Hz, 2H),
31 1.39 (t, J = 7.2 Hz, 3H), 1.36 (s, 18H).

32 Ethyl
33 2-Fluoro-4-[(2'-methoxym thyl-3',5'-di-t-butylphenyl
34)carbamoyl]benzoate (Compound G₃)

1 To a mixture of O-methoxymethyl-3',5'-di-t-
2 butylsalicylic acid (Compound F₃, 150 mg, 0.51 mmol),
3 4-dimethylaminopyridine (142 mg, 0.61 mmol) and
4 ethyl 2-fluoro-4-aminobenzoate (Compound C₁, 102 mg,
5 0.56 mmol) in 5 ml of dry CH₂Cl₂, was added 1-(3-di-
6 methylaminopropyl)-3-ethylcarbodiimide hydrochloride
7 (117 mg, 0.61 mmol). The reaction mixture was
8 stirred at room temperature for 12 hours. Solvent
9 was evaporated in vacuo and the residue was
10 dissolved in ethyl acetate, then washed with brine,
11 water and dried over MgSO₄. After filtration,
12 solvent was removed and the residue was purified by
13 column chromatography (ethyl acetate/hexane 1/3) to
14 give the title compound (58 mg). ¹H NMR δ 8.97 (b,
15 1H), 7.94 (t, J = 8.37 Hz, 1H), 7.78 (d, J = 2.7 Hz,
16 1H), 7.61 (d, J = 13.0 Hz, 1H), 7.56 (d, J = 2.6 Hz,
17 1H), 7.35 (d, J = 8.7 Hz, 1H), 5.00 (s, 2H), 3.53
18 (s, 3H), 4.38 (q, J = 7.1 Hz, 2H), 1.47 (s, 9H),
19 1.39 (t, J = 7.2 Hz, 3H), 1.33 (s, 9H).

20 Ethyl

21 2-Fluoro-4-[(2'-hydroxy-3',5'-di-t-butylphenyl)carbamoyl]benzoate (Compound 47)

22
23 To a solution of ethyl 2-fluoro-4-[(2'-
24 methoxymethyl-3',5'-di-t-butylphenyl)carbamoyl]benzo-
25 ate (Compound G₃, 34 mg, 0.07 mmol) in 1 ml of THF
26 were added 10 drops of HOAc. The reaction mixture
27 was heated to reflux for 12 hours. Solvent was
28 removed and ethyl acetate was added. The solution
29 was washed with NaHCO₃ (sat.), brine, water and dried
30 over MgSO₄. Solvent was removed in vacuo to give an
31 oil. The oil was allowed to be exposed to the
32 atmosphere for 12 hours during which time crystals
33 formed. The crystals were collected and washed
34 several times with hexane to afford the title

1 compound as a white solid (13.5 mg). ¹H NMR δ 10.73
2 (s, 1H), 7.98 (d, J = 2.56 Hz, 1H), 7.88 (b, 1H),
3 7.75 (t, J = 8.26 Hz, 1H), 7.60 (d, J = 2.44 Hz,
4 1H), 7.32 (dd, J = 12.3, 2.0 Hz, 1H), 7.02 (dd, J =
5 8.6, 2.0 Hz, 1H), 4.35 (q, J = 7.2 Hz, 2H), 1.39 (s,
6 9H), 1.37 (t, J = 7.2 Hz, 3H), 1.5 (s, 9H).

7 2,6-Difluoro-4-[(2',6'-di-t-butylpyrid-4'yl)carbamoyl]
8 benzoic Acid (Compound 50)

9 To 2,6-di-t-butylisonicotinic acid (Compound C,
10 20 mg, 0.085 mmol) was added 1 ml of SOCl₂. The
11 mixture was heated under reflux for 2 hours. After
12 cooling to room temperature, excess SOCl₂ was removed
13 and the residue was dissolved in 2 ml of CH₂Cl₂. To
14 this solution was added methyl 2,6-difluoro-4-amino-
15 benzoate (Compound H₁, 16 mg, 0.085 mmol) and
16 triethylamine (0.015 ml, 0.1 mmol). The reaction
17 mixture was kept at room temperature for 2 hours and
18 then concentrated to dryness. The residue was
19 purified by column chromatography with ethyl
20 acetate/hexane (1/10) to yield the methyl ester of
21 the title compound. This was saponified according
22 to the general procedure (see below) to give the
23 title compound as a colorless solid. ¹H NMR δ 7.44
24 (s, 2H), 7.40 (d, J = 11.8 Hz, 2H) 1.37 (s, 18H).

25 2,6-Difluoro-4-[(3',5'-di-t-butylphenyl)carbamoyl]
26 benzoic Acid (Compound 52)

27 Using the same procedure as for the preparation
28 of 2,6-difluoro-4-[(2',6'-di-t-butylpyrid-
29 4'yl)carbamoyl]benzoic acid (Compound 50) but using
30 3,5-di-t-butylbenzoic acid (37 mg, 0.16 mmol) and
31 methyl 2,6-difluoro-4-aminobenzoate (Compound H₁, 29
32 mg, 0.16 mmol), the title compound was obtained as
33 colorless crystals. ¹H NMR δ 7.92 (b, 1H) 7.60 (m,
34 3H), 7.42 (d, J = 10.0 Hz, 2H), 1.38 (s, 18H).

1 2-Nitro-4-[(2',6'-di-t-butylpyrid-4'-yl)carbamoyl]be
2 nzoic Acid (Compound 54)

3 Using the same procedure as for the preparation
4 of 2,6-difluoro-4-[(2',6'-di-t-butylpyrid-
5 4'yl)carbamoyl]benzoic acid (Compound 50) but using
6 2,6-di-t-butylisonicotinic acid (40 mg, 0.17 mmol)
7 and methyl 2-nitro-4-aminobenzoate (Compound F₁, 33
8 mg, 0.17 mmol), the title compound was obtained as a
9 light yellow oil. ¹H NMR δ (acetone-d₆) 10.25 (b,
10 1H), 8.32 (s, 1H), 7.97 (d, J = 8.1 Hz, 1H), 7.93
11 (b, 1H), 7.70 (s, 2H), 1.36 (s, 18H).

12 Methyl 2-nitro-4-[(4'-bromo-5',6',7',8'-tetrahydro-
13 5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]be
14 nzoate (Compound 25)

15 Using the same procedure as for the synthesis of
16 Compound 1, but using Compound F and Compound F₁, the
17 desired product was obtained as a white solid.
18 ¹H NMR δ 9.24 (b, 1H), 9.23 (d, J = 1.8 Hz, 1H), 7.92
19 (dd, J = 8.4, 2.4, Hz, 1H), 7.87 (d, J = 2.1 Hz,
20 1H), 7.84 (d, J = 2.1 Hz, 1H), 7.80 (d, J = 8.7 Hz,
21 1H), 3.91 (s, 3H), 1.75 (m, 2H), 1.65 (m, 2H), 1.58
22 (s, 3H), 1.33 (s, 3H).

23 General procedure for the syntheses of benzoic
24 acid derivatives by hydrolyzing the corresponding
25 methyl or ethyl esters.

26 To a solution of ester (3.0 mmol) in 20 ml of
27 EtOH was added 5 ml of 1 N NaOH in water. The
28 reaction mixture was stirred at room temperature for
29 overnight and neutralized with 10% HCl to pH=5. The
30 alcohol was removed by evaporation and the aqueous
31 layer was extracted with ethyl acetate (3x10ml).
32 The combined ethyl acetate layers were washed with
33 NaHCO₃ (sat.), brine and dried over MgSO₄. Aft r
34 concentration, the desired acid was obtained which

1 could be recrystallized in ethyl acetate or in
2 acetonitrile.

3 2-Fluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetr
4 amethylnaphthalen-2'-yl)carbamoyl]benzoic Acid
5 (Compound 2)

6 ¹H NMR δ (acetone-D₆) 9.86 (b, 1H), 7.95 (m, 3H),
7 7.75 (dd, J = 7.9, 2.2 Hz, 1H), 7.62 (dd, J = 8.5,
8 1.6 Hz, 1H), 7.50 (d, J = 8.3 Hz, 1H), 1.73 (s, 4H),
9 1.32 (s, 6H), 1.30 (s, 6H).

10 2-Fluoro-4-[(4'-bromo-5',6',7',8'-tetrahydro-5',5',8
11 ',8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic
12 Acid (Compound 4)

13 ¹H NMR δ (acetone-D₆) 9.97 (b, 1H), 8.04 (d, J = 1.89
14 Hz, 1H), 8.01 (d, J = 1.90 Hz, 1H), 7.95 (t, J =
15 8.55 Hz, 1H), 7.90 (dd, J = 12.28, 2.0 Hz, 1H), 7.59
16 (dd, J = 8.67, 1.50 Hz, 1H), 1.76 (m, 4H), 1.58 (s,
17 6H), 1.35 (s, 6H).

18 2-Fluoro-4-[(3'-hydroxy-5',6',7',8'-tetrahydro-5',5'
19 ,8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic
20 Acid (Compound 6)

21 ¹H NMR (acetone-D₆) δ 11.3 (b, 1H), 10.2 (b, 1H),
22 7.94 (m, 2H), 7.85 (dd, J = 11.4, 1.95 Hz, 1H), 7.53
23 (dd, J = 6.59, 2.08 Hz, 1H), 6.94 (s, 1H), 2.85 (b,
24 1H), 1.70 (s, 4H), 1.29 (s, 6H), 1.28 (s, 12H).

25 2-Fluoro-4-[(8'-bromo-4',4'-dimethylchroman-6'-yl)ca
26 rbamoyl]benzoic Acid (Compound 8)

27 ¹H NMR (acetone-d₆) δ 9.87 (b, 1H), 8.04 (d, J = 2.1
28 Hz, 1H), 8.03 (d, J = 2.1 Hz, 1H), 7.94 (t, J = 8.66
29 Hz, 1H), 7.91 (dd, J = 13.8, 2.0 Hz, 1H), 7.57 (dd,
30 J = 8.6, 2.0 Hz, 1H), 4.37 (t, J = 5.44 Hz, 2H),
31 1.92 (t, J = 5.44 Hz, 2H), 1.40 (s, 6H).

32 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-bromochroman
33 -6'-yl)carbamoyl]benzoic Acid (Compound 10)

34 ¹H NMR δ (acetone-d₆) 9.87 (b, 1H), 8.06 (d, J = 2.2

1 Hz, 1H), 8.04 (d, J = 2.1 Hz, 1H), 7.94 (t, J = 8.54
2 Hz, 1H), 7.91 (dd, J = 14.0, 2.0 Hz, 1H), 7.59 (dd,
3 J = 8.5, 2.3 Hz, 1H), 1.96 (s, 2H), 1.42 (s, 6H),
4 1.41 (s, 6H).

5 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-trifluoro-
6 methylchroman-6'-yl)carbamoyl] benzoic Acid
7 (Compound 12)

8 ¹H NMR (acetone-d₆) δ 10.02 (b, 1H), 8.31 (s, 1H),
9 8.09 (s, 1H), 7.92 (m, 2H), 7.56 (d, J = 7.69 Hz,
10 1H), 2.00 (s, 2H), 1.44 (s, 6H), 1.41 (s, 6H).

11 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-azidochroman
12 -6'-yl)carbamoyl]benzoic Acid (Compound 14)

13 ¹H NMR δ 8.03 (t, J = 8.4 Hz, 1H), 7.87 (b, 1H), 7.79
14 (dd, J = 13, 2.0 Hz, 1H), 7.64 (d, J = 2.2 Hz, 1H),
15 7.32 (dd, J = 8.66, 1.9 Hz, 1H), 7.22 (d, J = 2.1
16 Hz, 1H), 1.91 (s, 2H), 1.45 (s, 6H), 1.41 (s, 6H).

17 2,6-Difluoro-4-[(2',2',4',4'-tetramethyl-8'-
18 trifluoromethylchroman-6'-yl)carbamoyl]benzoic acid
19 (Compound 16)

20 ¹H NMR (acetone-d₆) δ 8.30 (d, J = 2.3 Hz, 1H), 8.06
21 (d, J = 2.2 Hz, 1H), 7.59 (d, J = 10.32 Hz, 2H),
22 1.954 (s, 2H), 1.44 (s, 6H), 1.41 (s, 6H).

23 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-iodochroman-
24 6'-yl)carbamoyl]benzoic Acid (Compound 18)

25 ¹H NMR δ (acetone-d₆) 10.0 (b, 1H), 8.24 (s, 1H),
26 8.07 (s, 1H), 7.94 (m, 2H), 7.57 (d, J = 8.67 Hz,
27 1H), 1.95 (s, 2H), 1.41 (s, 12H).

28 2-Fluoro-4-[(2',2',4',4',8'-pentamethylchroman-6'-yl
29)carbamoyl]benzoic Acid (Compound 20) ¹H NMR δ

30 (acetone-d₆) 9.77 (b, 1H), 7.90 (m, 3H), 7.65 (d, J =
31 2.0 Hz, 1H), 7.56 (dd, J = 8.61, 2.0 Hz, 1H), 2.19
32 (s, 3H), 1.90 (s, 2H), 1.38 (s, 6H), 1.37 (s, 6H).

33 4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylna
34 phthalen-2'-yl)thiocarbamoyl]benzoic Acid (Compound

1 22)

2 ¹H NMR δ 9.08 (b, 1H), 8.17 (d, J = 8.61, 2H), 7.95
3 (b, 2H), 7.77 (b, 1H), 7.57 (dd, J = 8.1, 2.1 Hz,
4 1H), 7.37 (d, J = 8.2 Hz, 1H), 1.72 (s, 4H), 1.32
5 (s, 6H), 1.31 (s, 6H).

6 2-Fluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetr
7 amethylnaphthalen-2'-yl)thiocarbamoyl]benzoic Acid
8 (Compound 24)

9 ¹H NMR δ (acetone-d₆) 11.1 (b, 1H), 8.27 (b, J = 13.2
10 Hz, 1H), 8.02 (t, J = 8.3 Hz, 1H), 7.89 (s, 1H),
11 7.86 (d, J = 10.0 Hz, 1H), 7.62 (d, J = 8.3 Hz, 1H),
12 7.41 (d, J = 8.37 Hz, 1H), 1.72 (s, 4H), 1.30 (s,
13 12H).

14 2-Fluoro-4-[(3'-hydroxy-4'-bromo-5',6',7',8'-tetrahy
15 dro-5',5',8',8'-tetramethylnaphthalen-2'-
16 yl)carbamoyl]benzoic Acid (Compound 30)

17 A solution of ethyl 2-fluoro-4-[(3'-
18 methoxymet-hoxy-4'-bromo-5',6',7',8'-tetrahydro-5',5',
19 ',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoa
20 te (Compound S₁, 45 mg, 0.084 mmol) in 1 ml of EtOH
21 was added 1 ml of aqueous solution of NaOH (1M).
22 The reaction mixture was stirred at room temperature
23 for overnight and acidified to PH = 1 with 10% HCl.
24 EtOH was removed and ethyl acetate and more water
25 were added to the solution. The organic layer was
26 separated and washed with NaHCO₃, brine and dried
27 over MgSO₄. After filtration and concentration, the
28 reaction yielded 2-fluoro-4-[(3'-methoxymethoxy-
29 4'-bromo-5',6',7',8'-tetrahydro-5',5',8',8'-tetramet
30 hyl naphthalen-2'-yl)carbamoyl]benzoic acid as a
31 white solid. The methoxymethyl group was removed by
32 dissolving the white solid in 2 ml of MeOH and 3
33 drops of HCl (con.). After stirring for overnight,
34 the reaction mixtur was concentrated to dryness.

1 Th residue was partitioned between ethyl acetate
2 and water. The organic layer was separated, washed
3 with NaHCO_3 , brine and dried over MgSO_4 . After
4 filtration and concentration, the residual solid was
5 purified in a mini (pipette) column with ethyl
6 acetate /hexane (1/1) to give the title compound as
7 a white solid (5.0 mg).

8 ^1H NMR δ (acetone- d_6) 10.19 (b, 1H), 8.01 (s, 1H),
9 7.96 (t, $J = 8.6$ Hz, 1H), 7.76 (dd, $J = 11.2$; 2.0
10 Hz, 1H), 7.54 (dd, $J = 8.8$; 2.0 Hz, 1H), 1.75 (m,
11 2H), 1.65 (m, 2H), 1.61 (s, 6H), 1.32 (s, 6H).
12 2,6-Difluoro-4-[(3'-hydroxy-4'-bromo-5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic Acid (Compound 32)

13
14
15 Using the same procedure as for the synthesis of
16 2-fluoro-4-[(3'-hydroxy-4'-bromo-5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic acid (Compound 30) the title compound was
17
18
19 obtained as a white solid.

20 ^1H NMR δ (acetone- d_6) 10.23 (b, 1H), 8.01 (s, 1H),
21 7.52 (d, $J = 10.2$ Hz, 2H), 4.8 (b, 1H), 1.75 (m,
22 2H), 1.65 (m, 2H), 1.60 (s, 6H), 1.31 (s, 6H).
23 2,6-Difluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic Acid (Compound 34)

24
25
26 To 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-
27 2-naphthoic acid (43 mg, 0.19 mmol) was added 1 ml
28 of thionyl chloride. This mixture was refluxed for
29 2 h. Excess thionyl chloride was removed under
30 reduced pressure and the residue was dissolved in 2
31 ml of CH_2Cl_2 . To this solution was added methyl
32 4-amino-2,6-difluorobenzoate (Compound 31, 7 mg, 0.2
33 mmol) followed by 0.5 ml of pyridine. The reaction
34 mixture was stirred at room temperature for 4 h and

1 was concentrated under reduced pressure. The
2 residue was purified by column chromatography (ethyl
3 acetate/hexane 1/5) to give the methyl ester of the
4 desired product as a colorless oil.
5 ^1H NMR d 8.11 (d, $J = 1.9$ Hz, 1H), 8.05 (b, 1H), 7.86
6 (dd, $J = 6.2, 2.2$ Hz, 1H), 7.41 (m, 3H), 3.93 (s,
7 3H), 1.69 (s, 4H), 1.29 (s, 6H), 1.28 (s, 6H). This
8 colorless oil was hydrolyzed to the desired product
9 with NaOH/H₂O/EtOH according to the general
10 procedure.

11 ^1H NMR d (acetone-d₆) 9.74 (b, 1H), 7.95 (s, 1H),
12 7.70 (d, $J = 6.8$ Hz, 1H), 7.43 (d, $J = 8.4$ Hz, 3H),
13 1.71 (s, 4H), 1.29 (s, 6H), 1.28 (s, 6H).
14 2-Nitro-4-[(4'-bromo-5',6',7',8'-tetrahydro-5',5',8'
15 ,8',-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic
16 acid (Compound 26)

17 ^1H NMR δ (acetone-d₆): 10.16 (b, 1H), 8.42 (d, $J =$
18 2.0 Hz, 1H), 8.09 (dd, $J = 8.6; 2.1$ Hz, 1H), 8.06
19 (d, $J = 2.2$ Hz, 1H), 8.04 (d, $J = 2.2$ Hz, 1H), 7.93
20 (d, $J = 8.6$ Hz, 1H), 1.75 (m, 2H), 1.65 (m, 2H),
21 1.57 (s, 3H), 1.34 (s, 3H).
22 2-Fluoro-4-[(2',6'-di-t-butylpyrid-4'-yl)carbamoyl]b
23 enzoic Acid (Compound 42)

24 ^1H NMR δ (CD₃OD) 7.92 (t, $J = 8.36$ Hz, 1H), 7.82
25 (dd, $J = 12.82, 2.0$ Hz, 1H), 7.63 (s, 2H), 7.55 (dd,
26 $J = 8.7, 2.1$ Hz, 1H), 1.39 (s, 18H).
27 4-[(2',6'-Di-t-butylpyrid-4'-yl)carbamoyl]benzoic
28 acid (Compound 44)

29 ^1H NMR δ (CD₃OD) 8.02 (d, $J = 8.85$ Hz, 2H), 7.85
30 (d, $J = 8.85$ Hz, 2H), 7.63 (s, 2H), 1.40 (s, 18H).
31 2-Fluoro-4-[(3',5'-di-t-butyl)phenylcarbamoyl]benzoi
32 c acid (Compound 46)

33 ^1H NMR δ (CD₃OD) 7.92 (t, $J = 8.3$ Hz, 1H), 7.80
34 (dd, $J = 12.8, 2.0$ Hz, 1H), 7.79 (d, $J = 1.8$ Hz,

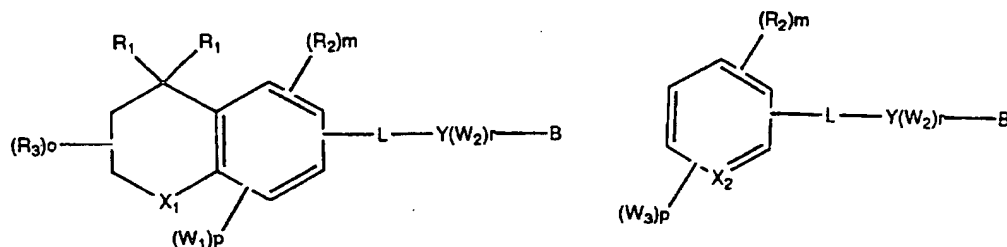
- 1 2H), 7.69 (t, J = 1.7 Hz, 1H), 7.57 (dd, J = 8.7,
2 2.1 Hz, 1H), 1.37 (s, 18H).
3 2-Fluoro-4-[(2'-hydroxy-3',5'-di-t-butyl)phenylcarba
4 moyl]benzoic acid (Compound 48)
5 ¹H NMR δ (acetone-d₆) 12.3 (b, 1H), 10.07 (b,
6 1H), 7.98 (t, J = 8.48 Hz, 1H), 7.80 (m, 2H), 7.58
7 (d, J = 2.3 Hz, 1H), 7.56 (dd, J = 8.8, 2.0 Hz, 1H),
8 1.44 (s, 9H), 1.31 (s, 9H).

WHAT IS CLAIMED IS:

- 1
2 1. A process of administering to a mammal a
3 retinoid compound which binds specifically or
4 selectively to a RAR_α retinoid receptors in
5 preference over RAR_β and RAR_γ retinoid receptors, for
6 the purpose of treating or preventing a disease or
7 condition which is responsive to treatment by RAR_α
8 specific or selective retinoid agonists.
- 9 2. A process in accordance with Claim 1 where
10 the RAR_α specific or selective retinoid compound
11 binds approximately 500 times stronger to RAR_α
12 retinoid receptors than to RAR_β and RAR_γ retinoid
13 receptors.
- 14 3. A process in accordance with Claim 1 where
15 the RAR_α specific or selective retinoid compound is
16 administered to a mammal for the treatment or
17 prevention of the disease or condition selected from
18 acute monocytic leukemia, cervical carcinoma,
19 myeloma, ovarian carcinomas, head and neck
20 carcinomas, proliferative vitreoretinopathy (PVR)
21 and age related macular degeneration (AMD).
- 22 4. A process in accordance with Claim 3 where
23 the RAR_α specific or selective retinoid compound is
24 administered in a dose of approximately 0.5 to 5 mg
25 per kg body weight per day.
- 26 5. A process in accordance with Claim 1 where
27 the RAR_α specific or selective retinoid compound is
28 administered to a mammal for the treatment or
29 prevention of the disease or condition selected from
30 actinic keratoses, arsenic keratoses, inflammatory
31 and non-inflammatory acne, psoriasis, ichthyoses,
32 eczema, atopic dermatitis, Darriers disease, lichen
33 planus, glucocorticoid damage, topical microbial
34 infection, skin pigmentation, age and photo damage

1 to the skin, premalignant and malignant
 2 hyperproliferative diseases, Kaposi's sarcoma,
 3 diseases of the eye, proliferative vitreoretinopathy
 4 (PVR), retinal detachment, dry eye and other
 5 corneopathies, cardiovascular diseases,
 6 dyslipidemias, prevention of post-angioplasty
 7 restenosis, diseases associated with human papilloma
 8 virus (HPV), inflammatory diseases,
 9 neurodegenerative diseases, improper pituitary
 10 function, insufficient hair growth, diseases
 11 associated with the immune system, and wound
 12 healing.

13 6. A process in accordance with Claim 1 where
 14 the RAR_n specific or selective retinoid compound has
 15 the formula (i) or the formula (ii)



30 formula (i)

31 formula (ii)

32 where X_1 is O or X_1 is $[C(R_1)_2]_n$ where n is an integer
 33 between 0 and 2;

34 R_1 is independently H or alkyl of 1 to 6
 carbons;

R_2 is independently hydrogen, or lower alkyl of

1 1 to 6 carbons;
2 R_1 is hydrogen, lower alkyl of 1 to 6 carbons or
3 F;
4 m is an integer having the value of 0 - 5;
5 o is an integer having the value of 0 - 4;
6 p is an integer having the value of 0 - 2;
7 r is an integer having the value 0 - 2;
8 X_2 is N or CH;
9 Y is a phenyl or naphthyl group, or heteroaryl
10 selected from a group consisting of pyridyl,
11 thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
12 thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said
13 phenyl, naphthyl and heteroaryl groups being
14 optionally substituted with one or two R_2 groups;
15 W_1 is a substituent selected independently from
16 the group consisting of F, Br, Cl, I, fluoro
17 substituted C_{1-6} alkyl, NO_2 , and OH, with the provisos
18 that:
19 (i) when the compound is in accordance with
20 formula (i) and Z is O then the sum of p and r is at
21 least 1 and W_1 is not a fluoro group in the 3
22 position of a tetrahydronaphthalene ring;
23 (ii) when the compound is in accordance with
24 formula (i) and r is zero and p is 1 and W_1 is OH
25 then the OH group is positioned α to the L group;
26 W_2 is a substituent selected independently from
27 the group consisting of F, Br, Cl, I, fluoro
28 substituted C_{1-6} alkyl, NO_2 , and OH;
29 W_3 is a substituent selected independently from
30 the group consisting of F, Br, Cl, I, C_{1-6} alkyl,
31 fluoro substituted C_{1-6} alkyl, NO_2 , and OH with the
32 proviso that wh n the compound is in accordance with
33 Formula 2 and X_2 is CH and r is 0 then p is not 0 and
34 at least one W_i group is not alkyl;

1 L is $-(C=Z)-NH-$ or $-NH-(C=Z)-$ Z is O or S,
2 and
3 B is COOH or a pharmaceutically acceptable salt
4 thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11} , CH_2OCOR_{11} ,
5 CHO , $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, $CR_7OR_{13}O$,
6 where R_7 is an alkyl, cycloalkyl or alkenyl group
7 containing 1 to 5 carbons, R_8 is an alkyl group of 1
8 to 10 carbons or trimethylsilylalkyl where the alkyl
9 group has 1 to 10 carbons, or a cycloalkyl group of
10 5 to 10 carbons, or R_8 is phenyl or lower
11 alkylphenyl, R_9 and R_{10} independently are hydrogen,
12 an alkyl group of 1 to 10 carbons, or a cycloalkyl
13 group of 5-10 carbons, or phenyl or lower
14 alkylphenyl, R_{11} is lower alkyl, phenyl or lower
15 alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent
16 alkyl radical of 2-5 carbons.

17 7. A process in accordance with Claim 6 where
18 the RAR_a specific or selective retinoid compound is
19 in accordance with formula (i).

20 8. A process in accordance with Claim 7 where
21 in the formula of the RAR_a specific or selective
22 retinoid compound X_1 is $[C(R_1)_2]_n$ and n is 1.

23 9. A process in accordance with Claim 8 where
24 in the formula of the RAR_a specific or selective
25 retinoid compound Y is phenyl.

26 10. A process in accordance with Claim 6 where
27 the RAR_a specific or selective retinoid compound is
28 in accordance with formula (ii).

29 11. A process in accordance with Claim 10 where
30 in the formula of the RAR_a specific or selective
31 retinoid compound Y is phenyl.

32 12. A process of administering to a mammal a
33 retinoid compound which binds specifically or
34 selectively to a RAR_a retinoid receptors in

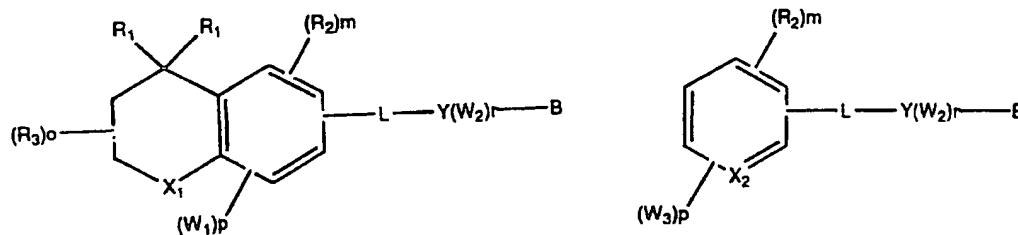
1 preference over RAR_{β} and RAR_{γ} retinoid receptors, for
2 the purpose of treating or preventing a disease or
3 condition which is responsive to treatment by RAR_{α}
4 specific or selective retinoid agonists, the
5 retinoid compound being specific or selective for
6 RAR_{α} retinoid receptors in preference over RAR_{β} and
7 RAR_{γ} retinoid receptors when in a binding assay the
8 K_d value of binding to RAR_{α} receptors is
9 approximately 500 times smaller than the K_d value for
10 binding to RAR_{β} and RAR_{γ} retinoid receptors.

11 13. A process in accordance with Claim 12 where
12 the RAR_{α} specific or selective retinoid compound is
13 administered to a mammal for the treatment or
14 prevention of the disease or condition selected from
15 actinic keratoses, arsenic keratoses, inflammatory
16 and non-inflammatory acne, psoriasis, ichthyoses,
17 eczema, atopic dermatitis, Darriers disease, lichen
18 planus, glucocorticoid damage, topical microbial
19 infection, skin pigmentation, age and photo damage
20 to the skin, premalignant and malignant
21 hyperproliferative diseases, Kaposi's sarcoma,
22 diseases of the eye, proliferative vitreoretinopathy
23 (PVR), retinal detachment, dry eye and other
24 corneopathies, cardiovascular diseases,
25 dyslipidemias, prevention of post-angioplasty
26 restenosis, diseases associated with human papilloma
27 virus (HPV), inflammatory diseases,
28 neurodegenerative diseases, improper pituitary
29 function, insufficient hair growth, diseases
30 associated with the immune system, and wound
31 healing.

32 14. A process in accordanc with Claim 13 where
33 the RAR_{α} specific or selective retinoid compound is
34 administered to a mammal for the treatment or

1 prevention of the disease or condition selected from
 2 acute monocytic leukemia, cervical carcinoma,
 3 myeloma, ovarian carcinomas, head and neck
 4 carcinomas, proliferative vitreoretinopathy (PVR)
 5 and age related macular degeneration (AMD).

6 15. A process in accordance with Claim 13 where
 7 the RAR_a specific or selective retinoid compound has
 8 the formula (i) or the formula (ii)



formula (i)

formula (ii)

where X_1 is O or X_1 is $[C(R_1)_2]_n$ where n is an integer
 between 0 and 2;

R_1 is independently H or alkyl of 1 to 6
 carbons;

R_2 is independently hydrogen, or lower alkyl of
 1 to 6 carbons;

R_3 is hydrogen, lower alkyl of 1 to 6 carbons or
 F;

m is an integer having the value of 0 - 5;

o is an integer having the value of 0 - 4;

p is an integer having the value of 0 - 2;

r is an integer having the value 0 - 2;

X_2 is N or CH;

1 Y is a phenyl or naphthyl group, or heteroaryl
2 selected from a group consisting of pyridyl,
3 thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
4 thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said
5 phenyl, naphthyl and heteroaryl groups being
6 optionally substituted with one or two R₂ groups;

7 W₁ is a substituent selected independently from
8 the group consisting of F, Br, Cl, I, fluoro
9 substituted C₁₋₆ alkyl, NO₂, and OH, with the provisos
10 that:

11 (i) when the compound is in accordance with
12 formula (i) and Z is O then the sum of p and x is at
13 least 1 and W₁ is not a fluoro group in the 3
14 position of a tetrahydronaphthalene ring;

15 (ii) when the compound is in accordance with
16 formula (i) and x is zero and p is 1 and W₁ is OH
17 then the OH group is positioned α to the L group;

18 W₂ is a substituent selected independently from
19 the group consisting of F, Br, Cl, I, fluoro
20 substituted C₁₋₆ alkyl, NO₂, and OH;

21 W₃ is a substituent selected independently from
22 the group consisting of F, Br, Cl, I, C₁₋₆alkyl,
23 fluoro substituted C₁₋₆ alkyl, NO₂, and OH with the
24 proviso that when the compound is in accordance with
25 Formula 2 and X₂ is CH and x is 0 then p is not 0 and
26 at least one W₃ group is not alkyl;

27 L is -(C=Z)-NH- or -NH-(C=Z)-

28 Z is O or S, and

29 B is COOH or a pharmaceutically acceptable salt
30 thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁,
31 CHO, CH(OR₁₂)₂, CHOR₁₃O, -COR₇, CR₇(OR₁₂)₂, CR₇OR₁₃O,
32 where R₇ is an alkyl, cycloalkyl or alk nyl group
33 containing 1 to 5 carbons, R₈ is an alkyl group of 1
34 to 10 carbons or trimethylsilylalkyl where the alkyl

1 group has 1 to 10 carbons, or a cycloalkyl group of
2 5 to 10 carbons, or R_9 is phenyl or lower
3 alkylphenyl, R_9 and R_{10} independently are hydrogen,
4 an alkyl group of 1 to 10 carbons, or a cycloalkyl
5 group of 5-10 carbons, or phenyl or lower
6 alkylphenyl, R_{11} is lower alkyl, phenyl or lower
7 alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent
8 alkyl radical of 2-5 carbons.

9 16. A process in accordance with Claim 15 where
10 the RAR_α specific or selective retinoid compound is
11 in accordance with formula (i).

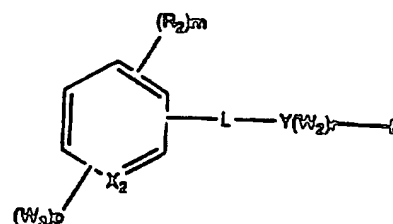
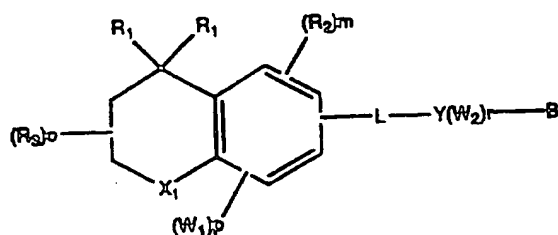
12 17. A process in accordance with Claim 15 where
13 the formula the RAR_α specific or selective retinoid
14 compound is in accordance with formula (ii).

15 18. A process of administering to a mammal a
16 retinoid compound which binds specifically or
17 selectively to a RAR_α retinoid receptors in
18 preference over RAR_β and RAR_γ retinoid receptors, for
19 the purpose of treating or preventing the disease or
20 condition selected from acute monocytic leukemia,
21 cervical carcinoma, myeloma, ovarian carcinomas,
22 head and neck carcinomas, proliferative
23 vitreoretinopathy (PVR) and age related macular
24 degeneration (AMD) the retinoid compound being
25 specific or selective for RAR_α retinoid receptors in
26 preference over RAR_β and RAR_γ retinoid receptors when
27 in a binding assay the K_d value of binding to RAR_α
28 receptors is approximately 500 times smaller than
29 the K_d value for binding to RAR_β and RAR_γ retinoid
30 receptors, the retinoid compound having the formula
31 (i) or the formula (ii)

32

33

34



formula (i)

formula (ii)

where X_1 is O or X_1 is $[C(R_1)_2]_n$, where n is an integer between 0 and 2;

R_1 is independently H or alkyl of 1 to 6 carbons;

R_2 is independently hydrogen, or lower alkyl of 1 to 6 carbons;

R_3 is hydrogen, lower alkyl of 1 to 6 carbons or F;

m is an integer having the value of 0 - 5;

o is an integer having the value of 0 - 4;

p is an integer having the value of 0 - 2;

r is an integer having the value 0 - 2;

X_2 is N or CH;

Y is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl, naphthyl and heteroaryl groups being optionally substituted with one or two R_2 groups;

W_1 is a substituent selected independently from the group consisting of F, Br, Cl, I, fluoro substituted C_{1-6} alkyl, NO_2 , and OH, with the provisos that:

(i) when the compound is in accordance with

1 formula (i) and Z is O then the sum of p and r is at
2 least 1 and W₁ is not a fluoro group in the 3
3 position of a tetrahydronaphthalene ring;

4 (ii) when the compound is in accordance with
5 formula (ii) and r is zero and p is 1 and W₁ is OH
6 then the OH group is positioned α to the L group;

7 W₂ is a substituent selected independently from
8 the group consisting of F, Br, Cl, I, fluoro
9 substituted C₁₋₆ alkyl, NO₂, and OH;

10 W₃ is a substituent selected independently from
11 the group consisting of F, Br, Cl, I, C₁₋₆alkyl,
12 fluoro substituted C₁₋₆ alkyl, NO₂, and OH with the
13 proviso that when the compound is in accordance with
14 Formula 2 and X₂ is CH and r is 0 then p is not 0 and
15 at least one W₃ group is not alkyl;

16 L is -(C=Z)-NH- or -NH-(C=Z)-

17 Z is O or S, and

18 B is COOH or a pharmaceutically acceptable salt
19 thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁,
20 CHO, CH(OR₁₂)₂, CHOR₁₃O, -COR₇, CR₇(OR₁₂)₂, CR₇OR₁₃O,
21 where R₇ is an alkyl, cycloalkyl or alkenyl group
22 containing 1 to 5 carbons, R₈ is an alkyl group of 1
23 to 10 carbons or trimethylsilylalkyl where the alkyl
24 group has 1 to 10 carbons, or a cycloalkyl group of
25 5 to 10 carbons, or R₈ is phenyl or lower
26 alkylphenyl, R₉ and R₁₀ independently are hydrogen,
27 an alkyl group of 1 to 10 carbons, or a cycloalkyl
28 group of 5-10 carbons, or phenyl or lower
29 alkylphenyl, R₁₁ is lower alkyl, phenyl or lower
30 alkylphenyl, R₁₂ is lower alkyl, and R₁₃ is divalent
31 alkyl radical of 2-5 carbons.

32 19. A process in accordance with Claim 18 where
33 the RAR_a specific or selective retinoid compound is
34 in accordance with formula (i), and Y is phenyl.

1 20. A process in accordance with Claim 19 where the
2 RAR_α specific or selective retinoid compound is
3 selected from the group consisting of:

4 ethyl 2-fluoro-4-[(5',6',7',8'-tetrahydro-
5 5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]be
6 nzoate;

7 2-fluoro-4-[(5',6',7',8'-tetrahydro-
8 5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]be
9 nzoic acid;

10 ethyl 2-fluoro-4-[(5',6',7',8'-tetrahydro-4'-
11 bromo-5',5',8',8'-tetramethylnaphthalen-2'-yl)carbam
12 oyl]benzoate;

13 2-fluoro-4-[(4'-bromo-5',6',7',8'-tetrahydro-
14 5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]be
15 nzoic acid;

16 ethyl
17 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-bromochroman
18 -6'-yl)carbamoyl]benzoate;

19
20 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-bromochroman
21 - 6'-yl)carbamoyl]benzoic acid;

22 ethyl 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-
23 trifluoromethylchroman-6'-yl)carbamoyl] benzoate;

24 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-
25 trifluoro-methylchroman-6'-yl)carbamoyl] benzoic
26 acid;

27 ethyl 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-
28 azidochroman-6'-yl)carbamoyl]benzoate;

29 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-
30 azidochroman- 6'-yl)carbamoyl]benzoic acid;

31 ethyl 2-fluoro-4-[(2', 2', 4', 4'-tetramethyl-
32 8'-iodochroman-6'-yl)carbamoyl]benzoat ;

33 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-
34 iodochroman-6'-yl)carbamoyl]benzoic acid;

1 ethyl 4-[(5',6',7',8'-tetrahydro-5',5',8',8'-
2 tetramethyl-2-naphthalenyl)thiocarbamoyl]benzoate,
3 and
4 4-[(5',6',7',8'-tetrahydro-5',5',8',8'-
5 tetramethylnaphthalen-2'-yl)thiocarbamoyl]benzoic
6 acid.

7 21. A process in accordance with Claim 18 where
8 the RAR_a specific or selective retinoid compound is
9 in accordance with formula (ii), and Y is phenyl.

10 22. A process in accordance with Claim 19 where
11 the RAR_a specific or selective retinoid compound
12 is:

13 ethyl 2-fluoro-4-[(2',6'-di-tert-butylpyrid-4'-
14 yl)carbamoyl]benzoate, or

15 2-fluoro-4-[(2',6'-di-t-butylpyrid-4'-
16 yl)carbamoyl]benzoic acid.

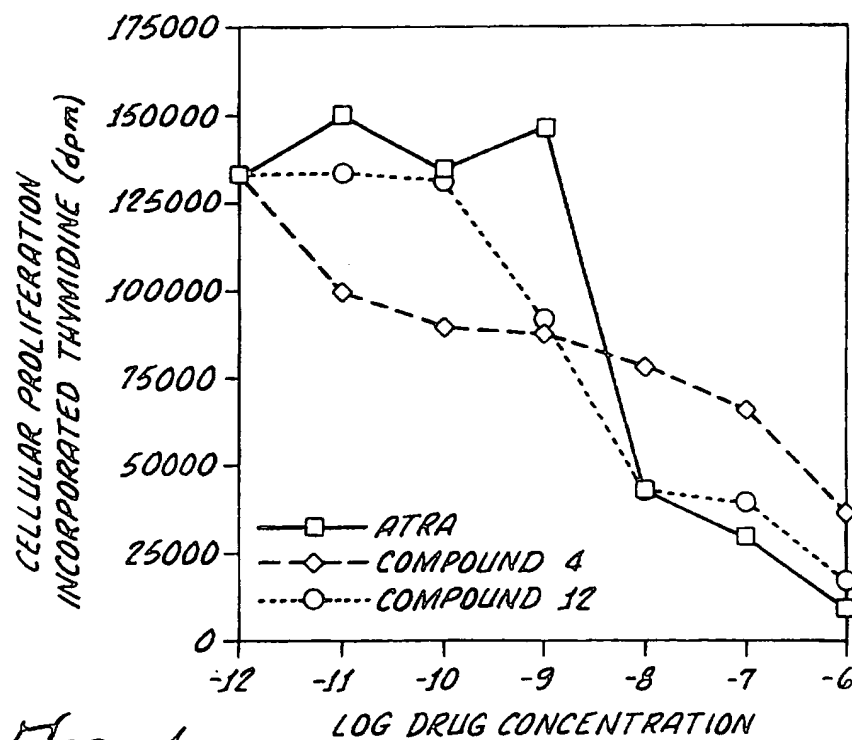


FIG. 1.

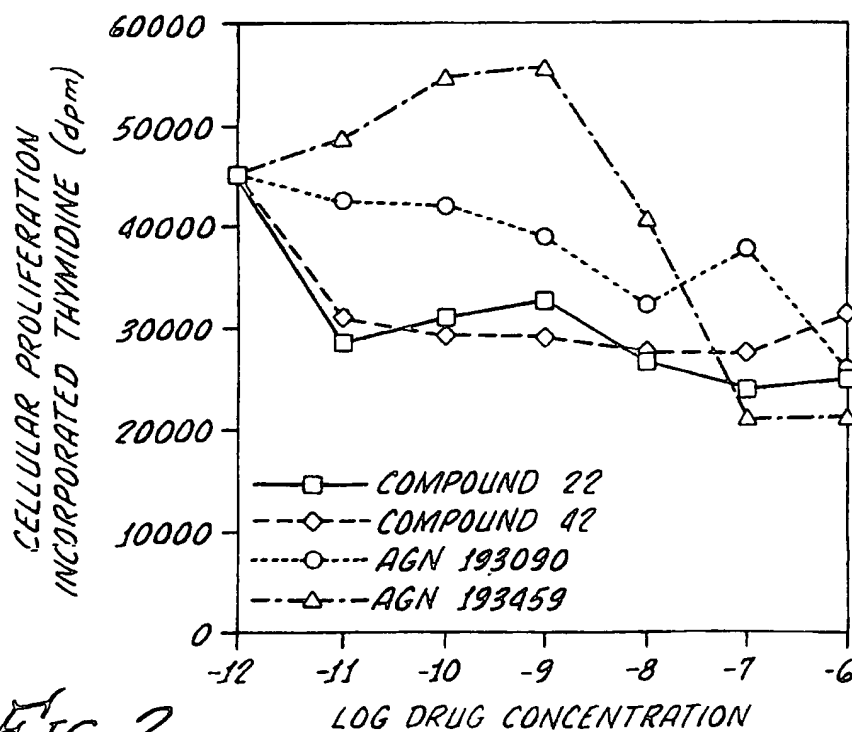
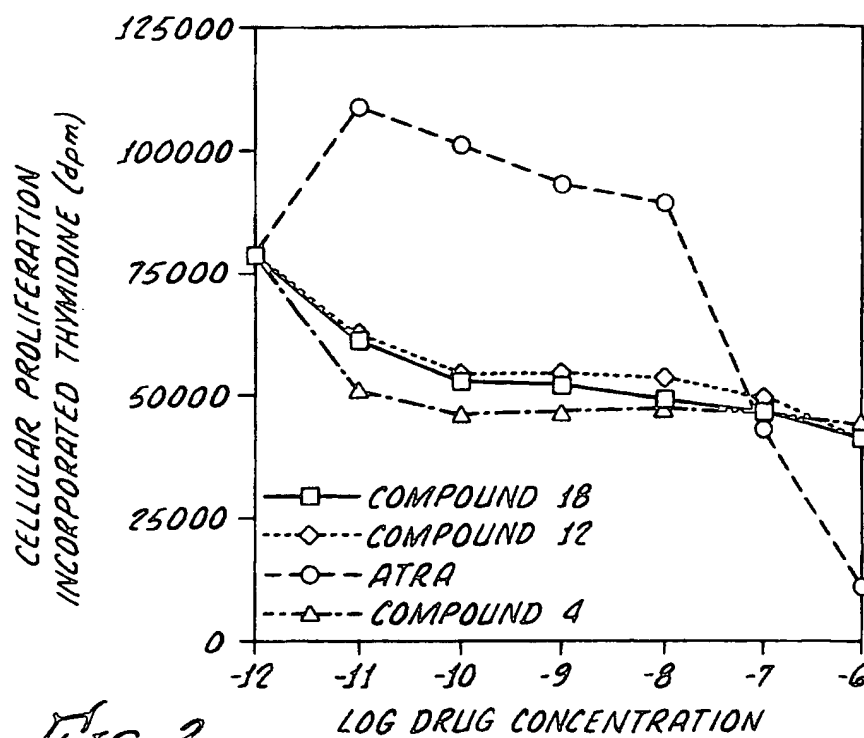
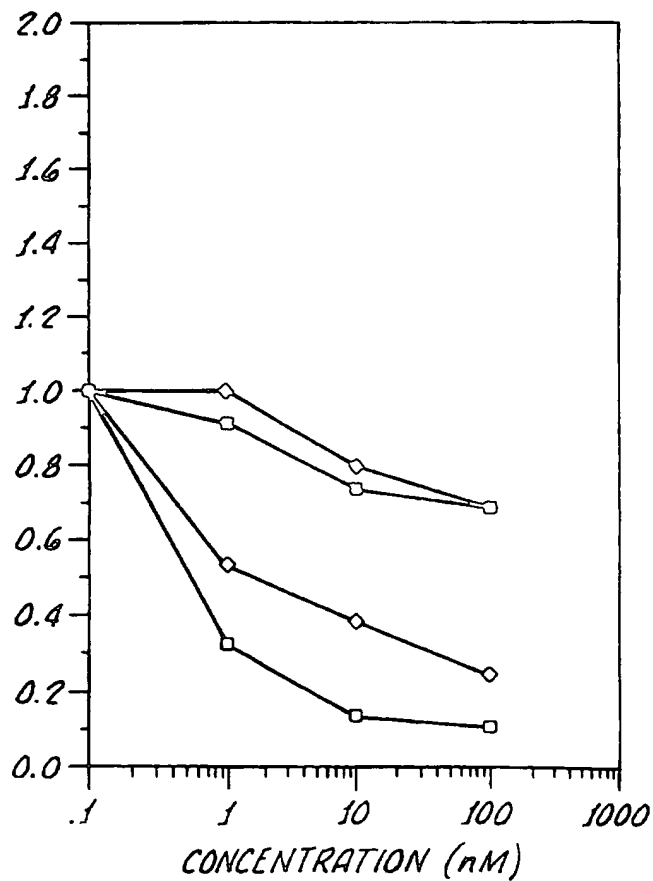


FIG. 2.

FIG. 3.FIG. 4.

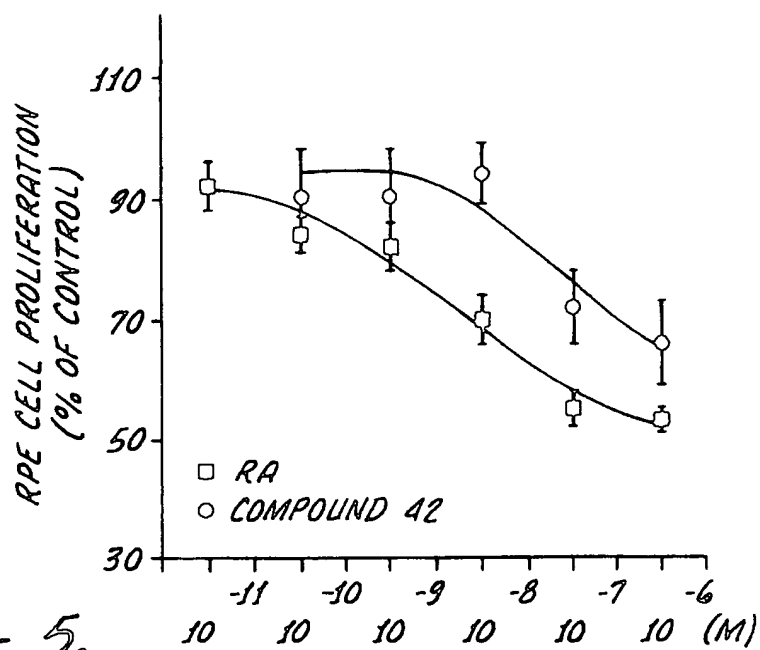


FIG. 5.

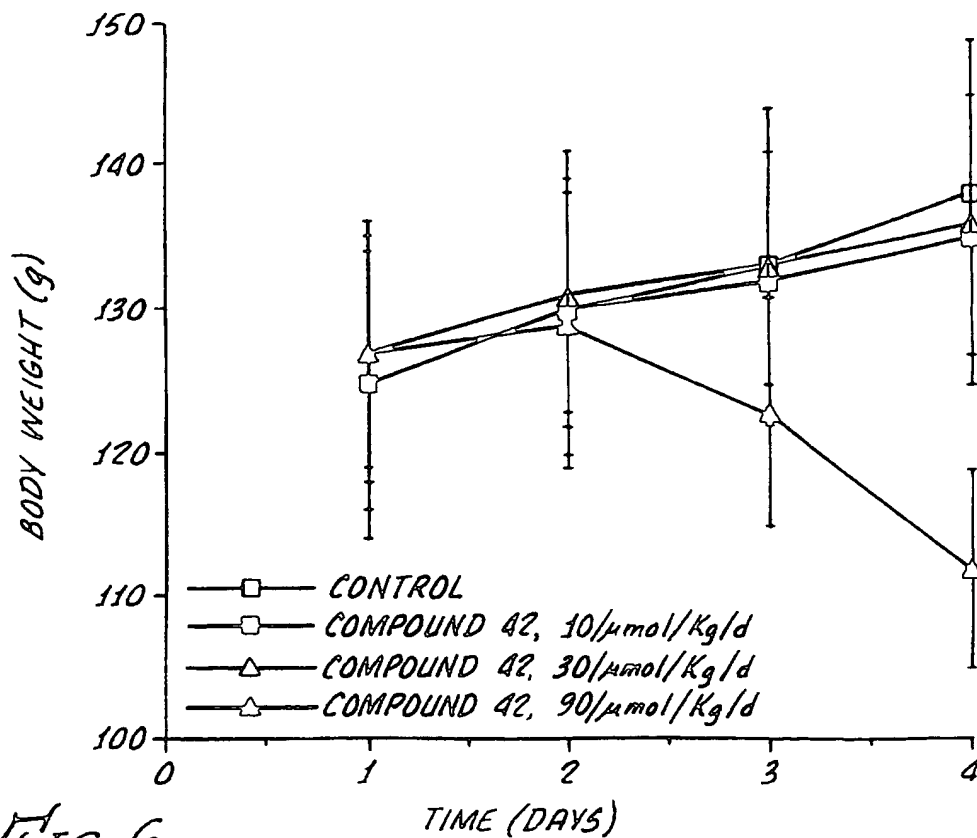
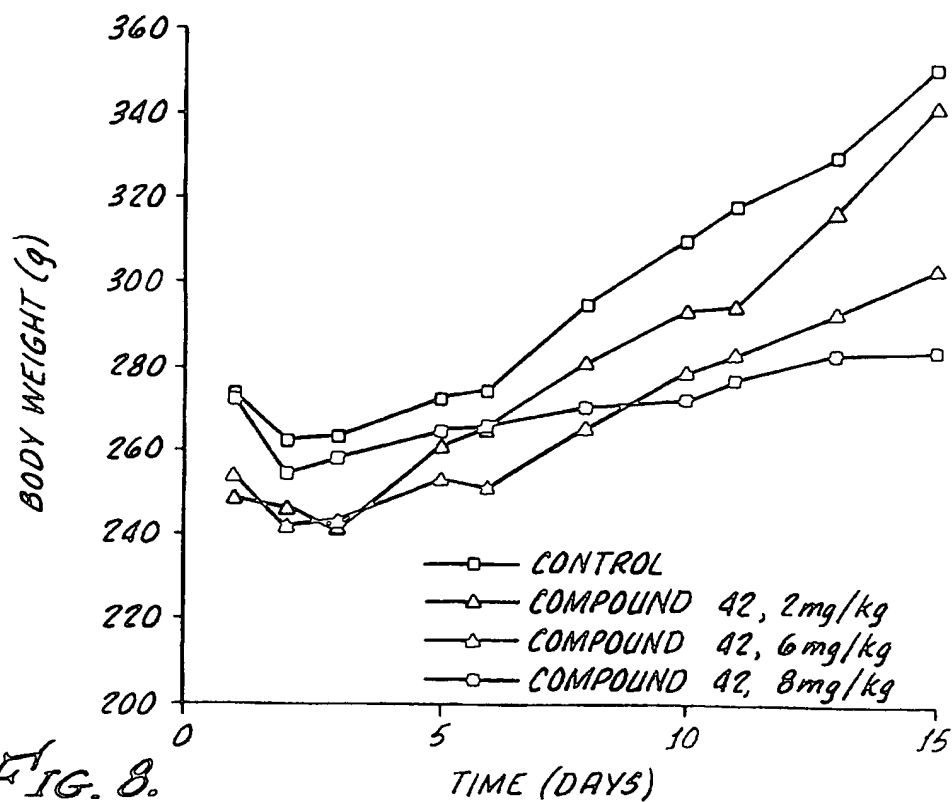
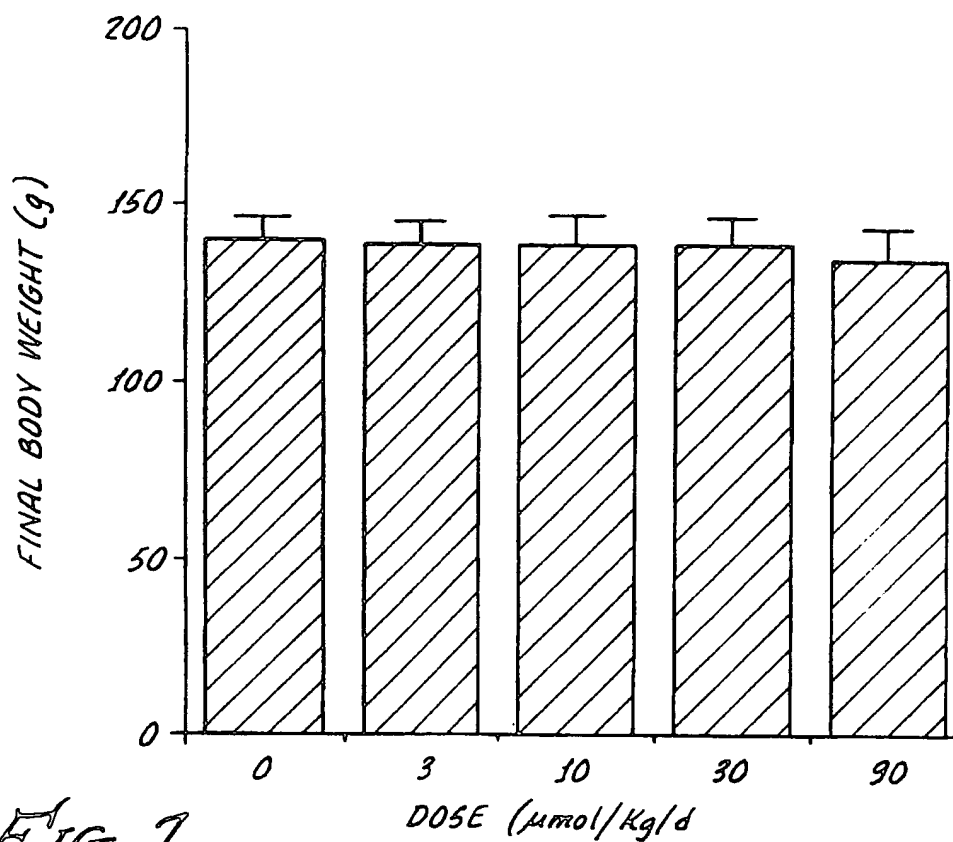


FIG. 6.





INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/19, 31/215, 31/34, 31/44	A3	(11) International Publication Number: WO 97/24116 (43) International Publication Date: 10 July 1997 (10.07.97)
(21) International Application Number: PCT/US96/20511 (22) International Filing Date: 16 December 1996 (16.12.96) (30) Priority Data: 08/580,553 29 December 1995 (29.12.95) US (71) Applicant: ALLERGAN [US/US]; 8301 Mars Drive, Waco, TX 76712 (US). (72) Inventors: TENG, Min; 2 Dove Street, Aliso Viejo, CA 92656 (US). DUONG, Tien, T.; Apartment 15C, 13 Bearpaw, Irvine, CA 92714 (US). CHANDRARATNA, Roshantha, A.; 25841 Empresa, Mission Viejo, CA 92691 (US). (74) Agents: BARAN, Robert, J. et al.; Allergan, Inc., 2525 Dupont Drive, T-2,2-E, P.O. Box 19534, Irvine, CA 92623-9534 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (86) Date of publication of the international search report: 13 November 1997 (13.11.97)
(54) Title: METHODS OF TREATMENT WITH COMPOUNDS HAVING RAR _α RECEPTOR SPECIFIC OR SELECTIVE ACTIVITY		
(57) Abstract Retinoid compounds which act specifically or selectively on RAR _α receptor subtypes in preference over RAR _β and RAR _γ receptor subtypes, possess desirable pharmaceutical properties associated with retinoids, and are particularly suitable for treatment of tumors, such as acute monocytic leukemia, cervical carcinoma, myeloma, ovarian carcinomas and head and neck carcinomas, without having one or more undesirable side effects of retinoids, such as inducement of weight loss, mucocutaneous toxicity, skin irritation and teratogenicity.		

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FR	France	MR	Mauritania	UZ	Uzbekistan
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/20511

A. CLASSIFICATION OF SUBJECT MATTER		
IPC 6 A61K31/19 A61K31/215 A61K31/34 A61K31/44		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
IPC 6 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 93 03713 A (SALK INST FOR BIOLOGICAL STUDI) 4 March 1993</p> <p>see page 9, line 4 - line 31; claims 1-15</p> <p>---</p> <p>-/--</p>	<p>1-4, 6-12, 14-22</p>
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
13 May 1997		30.09.97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016		Authorized officer Seegert, K

INTERNATIONAL SEARCH REPORT

Intern. Appl. Application No

PCT/US 96/20511

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL ABSTRACTS, vol. 121, no. 9, 1994 Columbus, Ohio, US; abstract no. 108128d, XP002030814 see abstract & YU, BAOXIN ET AL: "Synthesis of p-substituted benzoylaminobenzoic acid (methyl esters) and its differentiation induction activities of human promyelocytic leukemia cells HL-60" HUAXI YIKE DAXUE XUEBAO, vol. 25, no. 1, 1994, pages 30-34, ---	1-4, 6-12, 14-22
Y	DATABASE WPI Section Ch, Week 9416 Derwent Publications Ltd., London, GB; Class B05, AN 94-128759 XP002030803 & JP 06 072 866 A (CHUGOKU IGAKUKAGAKUIN YAKUBUTSU KENKYUSH), 15 March 1994 see abstract ---	1-4, 6-12, 14-22
Y	EP 0 514 269 A (CIRD GALDERMA) 19 November 1992 see page 3, line 3 - page 3, line 9; claims 1-21 especially claim 16, ex. 15 ---	1-4, 6-12, 14-22
Y	EP 0 350 846 A (HOFFMANN LA ROCHE) 17 January 1990 see page 5, line 43 - page 6, line 35; claims 1-18 ---	1-4, 6-12, 14-22
Y	US 5 420 145 A (SHUDO KOICHI) 30 May 1995 see column 3, line 65 - column 4, line 29; claims 1-4 ---	1-4, 6-12, 14-22
Y	EP 0 170 105 A (SHUDO KOICHI ;SUMITOMO PHARMA (JP); YOSHITOMI PHARMACEUTICAL (JP)) 5 February 1986 see claims 1-11 ---	1-4, 6-12, 14-22
P,Y	WO 96 32101 A (TAIHO PHARMACEUTICAL CO LTD ;SHIBATA JIRO (JP); WIERZBA KONSTANTY) 17 October 1996 see abstract ---	1-4, 6-12, 14-22

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INTERNATIONAL SEARCH REPORT

Inter. Application No

PCT/US 96/20511

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KAGECHIKA H ET AL: "RETINO BENZOIC ACIDS STRUCTURE-ACTIVITY RELATIONSHIPS OF AROMATIC AMIDES WITH RETINOIDAL ACTIVITY" JOURNAL OF MEDICINAL CHEMISTRY, vol. 31, no. 11, November 1988, pages 2182-2192, XP000608417 see tables I-VI see page 2187, left-hand column, last paragraph - page 2188, left-hand column ---	1-4, 6-12, 14-22
P,Y	MIN TENG ET AL: "Identification of a Retinoic Acid Receptor alpha Subtype Specific Agonist" J. MED. CHEM., vol. 39, no. 16, 2 August 1996, pages 3035-3038, XP000652115 see the whole document -----	1-4, 6-12, 14-22

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/20511

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See annex.

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-4, 6-12, 14-22 (partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 96 20511

FURTHER INFORMATION CONTINUED FROM PCT/ISA210

1. The use of a RAR alpha selective agonist for the prevention/treatment of acute monocytic leukemia, cervical carcinoma, myeloma, ovarian carcinomas, head and neck carcinomas (respective portions of Claims 1- 4, 6-12, 14 - 22)
2. The use of a RAR alpha selective agonist for the prevention/treatment of proliferative vitreoretinopathy (PVR), age related macular degeneration (AMD), diseases of the eye, retinal detachment, dry eye, other corneopathies (respective portions of Claims 1 - 22)
3. The use of a RAR alpha selective agonist for the prevention/treatment of actinic keratoses, arsenic keratoses, inflammatory and non-inflammatory acne, psoriasis, ichthyoses, eczema, atopic dermatitis, Darriers disease, lichen planus, skin pigmentation, age and photo damage to the skin, premalignant and malignant hyperproliferative diseases, Kaposi's sarcoma (respective portions of Claims 1, 2, 4 - 13, 15- 22)
4. The use of a RAR alpha selective agonist for the prevention/treatment of cardiovascular diseases (respective portions of Claims 1, 2, 4 - 13, 15- 22)
5. The use of a RAR alpha selective agonist for the prevention/treatment of dyslipidemias (respective portions of Claims 1, 2, 4 - 13, 15- 22)
6. The use of a RAR alpha selective agonist for the prevention of post-angioplasty restenosis (respective portions of Claims 1, 2, 4 - 13, 15- 22)

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 96 20511

FURTHER INFORMATION CONTINUED FROM PCT/ISA210

7. The use of a RAR alpha selective agonist for the prevention/treatment of diseases associated with human papilloma virus (HPV) (respective portions of Claims 1, 2, 4 - 13, 15- 22)
8. The use of a RAR alpha selective agonist for the for the prevention/treatment of inflammatory diseases (respective portions of Claims 1, 2, 4 - 13, 15- 22)
9. The use of a RAR alpha selective agonist for the prevention/treatment of neurodegenerative diseases (respective portions of Claims 1, 2, 4 - 13, 15- 22)
10. The use of a RAR alpha selective agonist for the prevention/treatment of improper pituitary function (respective portions of Claims 1, 2, 4 - 13, 15- 22)
11. The use of a RAR alpha selective agonist for the prevention/treatment of insufficient hair growth (respective portions of Claims 1, 2, 4 - 13, 15- 22)
12. The use of a RAR alpha selective agonist for the prevention/treatment of diseases associated with the immune system (respective portions of Claims 1, 2, 4 - 13, 15- 22)
13. The use of a RAR alpha selective agonist for wound healing (respective portions of Claims 1, 2, 4 - 13, 15- 22)

The search has been limited to the subject-matter of item 1.

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